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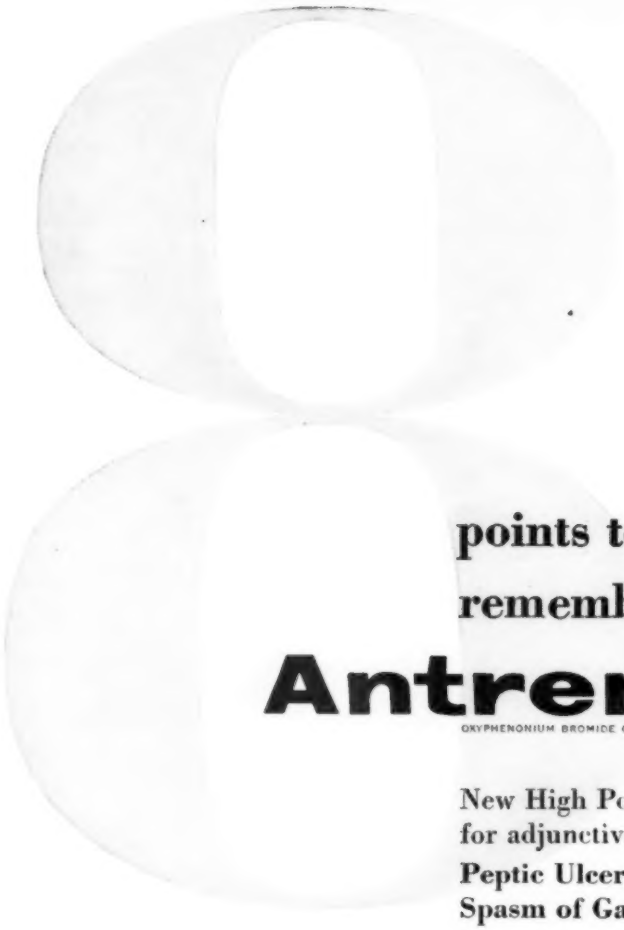

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RECENT CONCEPTS OF THE PATHOGENESIS OF ATHEROSCLEROSIS

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Atherosclerosis is one of the most important diseases in America. At least 200,000 victims die annually prematurely, or are subjected to some chronic illness as a direct result of this condition. Atherosclerosis is the term applied to thickening of the arterial intima, plaque formation resulting from the deposition of cholesterol and lipids, and the laying down of new connective tissue. It involves not only the large conducting elastic arteries such as the aorta, but also smaller arteries such as the coronaries and the cerebrals. It is the lipid laden intimal plaque which narrows the lumens of the coronary, cerebral, renal, and other arteries and thereby reduces the blood supply; the resulting dysfunction of the heart, brain, kidney and other tissues ends in invalidism or death.

The belief that atherosclerosis is an inevitable part of the aging process has discouraged research in this field. Although the pathogenesis of clinical atherosclerosis is still unsettled, recent research has contributed much to our knowledge, and from it has evolved the so-called "cholesterol concept of atherogenesis." A wave of enthusiasm has entered this field of study, since there is evidence that atherosclerosis may be a reversible process. The basic principle of this concept is that, without an altered cholesterol metabolism, little or no atherosclerosis will develop regardless of any other alteration in the arterial wall, including senescent changes. This may explain why atheromatous changes occur in some very young people and are absent in some very old people.

Clinical. The cholesterol concept of atherosclerosis has an extensive foundation in clinical research. For many years it has been known that widespread lipid and cholesterol deposition is the hallmark of the arterial lesion. Atherosclerosis appears more frequently in certain families and in stocky, pyknic, overweight individuals. Atherosclerosis is much more prevalent among peoples of the Western world, whose diet includes considerable amounts of fat and cholesterol, than among those whose diet is low in these constituents. A low incidence of

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atherosclerosis has been reported among the Chinese, Okinawans, Japanese and African Negroes in the 40–70 age group. There is little atherosclerosis among the native Ceylonese, whose diet is low in cholesterol, fat, protein and calories; whereas among the British and Dutch colonials of Ceylon, whose diet is similar to that of their homeland, the incidence of atherosclerosis in the same and older age groups is high. Moreover, the incidence of death and disability from atherosclerosis, including coronary disease, decreased in several European countries during World War II when there was a sharp reduction in the amount of cholesterol and fat in the diet. Accurate statistics available from Norway, Sweden and Finland prove this point. Overnutrition and obesity are generally associated with increased atherosclerosis, whereas undernutrition and disease are associated with decreased atherosclerosis.

That cholesterol and lipid metabolism are related to atherogenesis is suggested by the fact that certain clinical conditions frequently showing hypercholesterolemia and hyperlipemia are characterized by a relatively high incidence and severity of atherosclerosis. Such conditions include diabetes mellitus, hypothyroidism, familial hypercholesterolemia, xanthomatosis, nephrosis, and biliary obstruction. It is true that many patients who have atherosclerosis also show an increased plasma cholesterol level.

There is inconclusive evidence that the portion of cholesterol in the form of cholesterol esters is increased in clinical atherosclerosis and that the cholesterol phospholipid ratio is increased (1).

Patients who have coronary atherosclerosis without gross hypercholesterolemia have been demonstrated to have alterations in cholesterol metabolism and a xanthomatous tendency. Gofman and his colleagues (2) have found abnormalities in circulating cholesterol-bearing lipoproteins. They have demonstrated that there exists among the cholesterol and fat-bearing lipoproteins in the blood two particular classes of large lipoprotein molecules associated with atherosclerosis. These are designated as the SF 10–20 and SF 20–100 classes of lipoproteins, based upon their flotation rates in the analytic ultracentrifuge. These are the so-called "G" substances or giant molecules (3). There is some evidence that in atherosclerosis these "G" substances are not degraded into smaller ones of the SF 3–8 class, thought to be inactive in atherogenesis. The actual causal relationship of these comparatively large low-density lipoprotein molecules to atherosclerosis has not been fully demonstrated, but the arguments for the importance of the "G" particles in regard to atherosclerosis are: 1) The concentration of "G" in patients who have had a myocardial infarction tends to be higher than in persons who are clinically normal. 2) The rise in the "G" particles, allowing for age and sex difference, is consistent with the known incidence of atherosclerosis. 3) Patients with diseases frequently associated with early and severe atherosclerosis, such as diabetes mellitus or nephrosis, tend to have high concentrations of "G" in the serum. 4) In rabbits fed large amounts of cholesterol there is a high correlation between the concentration of "G" in the serum and the degree of atherosclerosis as graded by the pathologist. 5) The recurrence of clinical atherosclerotic accidents is higher in patients who

maintain a highly elevated lipoprotein level. Gofman also reports that a much stronger association of human atherosclerosis exists with the SF 10–20 and SF 20–100 lipoprotein levels than with serum cholesterol levels.

The study by Keys (4) on 482 clinically normal men failed to reveal a significant correlation between dietary cholesterol intake and serum cholesterol levels. Moreover, from the evidence he has made available it would appear that the concentration of total cholesterol has at least as much significance as has "G" in atherogenesis.

Cholesterol-containing colloidal aggregates are complex structures in respect to size, configuration and composition. Their constituents are not only the other plasma lipids, phospholipids and fatty acids but also proteins. Ahrens and Kunkel (5) have emphasized that a relationship appears to exist between the fixation of lipid in intimal cells and decreased phospholipid cholesterol ratios. They feel that the plasma cholesterol phospholipid ratio is more important than the concentration of either of the individual lipids in determining the presence or absence of atherosclerosis. The cholesterol phospholipid ratio is increased in most patients with atherosclerosis, and this results in a decreased ability to hold cholesterol in solution.

Moreton and his group of research workers (6) believe that the development of atherosclerosis is related to the large particle size of newly absorbed lipids (chylomicrons appearing in the plasma) and to the concentration and duration of the chylomicronemia following fat-rich meals. He postulated that there was a rise in circulating lipids of large size which were subject to phagocytosis by intimal macrophages, with the formation of intimal foam-cell plaques.

Experimental. Atherosclerosis does not occur spontaneously to any significant extent in the ordinary laboratory or domestic animal except in the chicken, which shows atheromatosis similar to that seen in man. As far back as forty years ago atheromatosis was produced experimentally in the rabbit. Hypercholesterolemia, hyperlipemia and atherosclerosis have been produced in the chicken by administering stilbestrol (7). Five years ago Steiner and Kendall (8) by means of cholesterol-thiouracil feeding in dogs, produced atherosclerosis which closely resembled human atheromatosis. Other animals in which atherosclerosis has been produced are the guinea pig, hamster and rat. Atherosclerosis has also been reported in the monkey given pyridoxine-deficient diet.

Experimentally, hypercholesterolemia, hyperlipemia and atherosclerosis are enhanced by increased amounts of cholesterol and fat in the diet (9). Experimental pancreatic diabetes, experimental hypothyroidism and liver damage by carbon tetrachloride have each been shown to augment experimental atherosclerosis. The cholesterol phospholipid ratio, the beta lipoproteins, and the SF 10–20 lipoproteins are increased in the plasma. Cortisone, DCA and ACTH have each been shown to increase the severity of experimental cholesterol atherosclerosis (10). Hypertension has been shown to enhance the production of experimental atherosclerosis. Local factors have also been shown to play a role in determining the site of experimental atheroma formation. Thus, local injury to the wall of the aorta predisposes this area to subsequent cholesterol atheromatous deposition.

Moreover, immobilization of a segment of arterial wall predisposes to atheroma formation in this region. Research findings in experimental atherosclerosis point strongly to altered cholesterol and lipid metabolism as an important basic factor in the pathogenesis of clinical atherosclerosis.

The laboratory has also been used as a testing ground for therapy in the study of atherosclerosis. Some of the findings are as follows:

1. Regression of lesions has been demonstrated in rabbits and chicks rendered atherosclerotic by cholesterol feeding, when such animals are returned to normal diets.

2. Intravenous administration of heparin has been shown to decrease experimental cholesterol atherosclerosis.

3. Intravenous injections of such detergents as Triton A-20 not only increase plasma phospholipids and decrease the cholesterol phospholipid ratio but also decrease the severity of experimental cholesterol atherosclerosis.

4. Desiccated thyroid has a partial inhibitory effect on experimental cholesterol atherosclerosis, as do lecithin and potassium thiocyanate.

5. Potassium iodide has no demonstrable effect.

6. Estrogens may decrease experimental coronary atherosclerosis in the chick.

7. Extensive and numerous studies have been carried out on the effect of lipotropic substances such as choline, inositol and methionine; the evidence is unequivocal that these lipotropic substances have no therapeutic value in experimental cholesterol atherosclerosis (11).

Diagnosis. Believing, then, that atherosclerosis is a process which can be arrested, what criteria can we use to make the early diagnosis of atherosclerosis and prevent the complications of this disease? We rely on the following: 1) Heredity. A family history of hypertension, coronary artery occlusion, diabetes mellitus and familial hyperlipemia is significant. 2) A history indicating vascular disease, *e.g.*, (a) cerebrovascular accidents as manifested by either a cerebral thrombosis or a hemorrhage, (b) cerebral arteriosclerosis as seen in patients in the premature senile group, pseudobulbar palsies and Parkinson's syndrome, (c) cardiovascular manifestations of coronary insufficiency, including angina pectoris, myocardial infarction, congestive heart failure, and various arrhythmias which are due to coronary insufficiency, (d) peripheral vascular insufficiency, such as is found in arteriosclerosis obliterans and in atherosclerotic aneurysms. 3) An electrocardiogram. Primary T-wave changes of the coronary type, incomplete or complete right or left bundle-branch block, or other defects of intraventricular conduction may be significant; if QRS alterations, with or without T-wave changes suggesting old myocardial infarction, are seen they are indicative of coronary arteriosclerosis. If the electrocardiogram shows no abnormalities, the hypoxemic test may be helpful. 4) Blood chemistry studies in relation to cholesterol, phospholipids, lipids and lipoproteins; these are of diagnostic value but are not conclusive. There are laboratories today that are anxious to measure the level of "G" particles, but until evidence is more conclusive or the methods are improved so that there will not exist such an overlapping of values between the non-atherosclerotic and atherosclerotic individuals,

this method should not be relied on too greatly. The total blood cholesterol level is still our best guide. 5) Diagnostic X-ray examination. In view of the frequent involvement of the abdominal aorta in atherosclerosis, a roentgenogram of the abdomen may reveal calcium deposits in atheromatous plaques in the aorta or elsewhere. 6) Physical examination. It is important to remember that pipestem radial arteries and tortuous temporal arteries are evidences of medial or Mönckeberg's sclerosis, which is not necessarily associated with atherosclerosis. Physical findings may be entirely negative.

Treatment. What can be done to prevent or treat atherosclerosis? The only proven measures are:

I. Diet. Data on the effect of diet on human atherosclerosis are both meager and unsatisfactory, but what evidence there is suggests that some measure of control of the development of atherosclerosis in man may be achieved by curtailing the total caloric intake and limiting both animal and vegetable fats and probably cholesterol (12). Keys (13) recommends a sharp reduction in all dietary fats. He would allow an ordinary amount of eggs and milk in cooking, skimmed milk with cereals and as a beverage, a good daily serving of lean meat or fish, and a boiled or poached egg for Sunday. Butter, cream, oleomargarine, salad oil, mayonnaise, fried foods, gravy, ice cream, chocolate, and pastries made with shortening are all forbidden. Periodic gorging should be avoided. Should it be recommended that a patient who has clinical evidence of atherosclerosis have his diet sharply restricted in cholesterol and fat? Katz (14) says no, except when a person is overweight or has had two myocardial infarcts. Keys (13) says yes. Page (15) says no. Gofman (3) believes that atherogenesis can be suppressed by diet. The answers to this question probably will be undecided for some time. In our own practice we have felt that a low-fat low-cholesterol diet has been worthwhile after a myocardial infarction.

II. Restriction of the body weight to about that considered standard for the given height at age 25. Obesity must be avoided.

III. Drugs. These consist of:

1. Vasodilating nitrites and xanthine derivatives to relieve the symptoms of angina, a complication of coronary atherosclerosis.
2. Sympathetic blocking drugs, in the treatment of intermittent claudication.
3. Established measures for reducing blood pressure, if hypertension is present.
4. Should one use lipotrophic drugs? There is no satisfactory evidence that these expensive substances have any effect in the prevention or treatment of atherosclerosis. The present view that these drugs are inert will have to be accepted.
5. Thyroid substance is theoretically of some value, but it is necessary to use caution in giving this drug to a patient with coronary atherosclerosis.
6. Heparin. Since this drug used intravenously lowers the plasma lipoprotein fraction, it has been given a clinical trial in relieving angina

pectoris. We are trying heparin intravenously in selected cases. Both clinical and laboratory findings justify its use.

7. Alcohol. There is no substantial evidence that alcohol aids in atherogenesis or that it dissolves the lesions once they are present, except in concentrations used in histologic preparations. Page (15) states "It does provide, however, a good caloric substitute for a lipid poor diet, and the unpalatability of the diet might be a good reason for drinking."

CONCLUSIONS

We have reviewed the progress made in the concepts of the pathogenesis of atherosclerosis and have presented the supporting clinical and laboratory data. Methods of diagnosis and therapy are outlined.

In spite of all the recent studies and advances, the problem is still unsolved, although progress is encouraging.

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THE ROLE OF ARTERIAL DISEASES IN CLINICAL MEDICINE

Some Comments on Classification of Arteriopathies

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Owing to improved methods of examining the heart, cardiac changes are easily recognized, readily classified and consequently more efficiently treated. Gone are the days when most patients, for example, suffered from "chronic myocarditis."

With attention thus focused on the heart as a separate entity, the common diseases of the vascular tree have unfortunately not been viewed with equal diligence. The role of arteriopathies, not only in heart disease but especially in diseases affecting other vital organs such as the brain, eye, kidney and liver have not been sufficiently emphasized or clinically evaluated.

As with "chronic myocarditis" of a quarter of a century ago, "arteriosclerosis" —a catch basket of arteriopathies—lacks the clinical specificity warranted by scientific data now available (1).

From the first national meeting of the American Society for the Study of Arteriosclerosis it became evident that a tentative classification of the various arterial diseases included under the generic term "arteriosclerosis" was essential. The very make-up of the membership of this society—clinicians, pathologists, biochemists, cyto-biologists, pharmacologists and bio-physicists—indicates widespread interest in the complexity of the problem.

In view of the heterogeneous approach, a special committee on nomenclature[1] was, therefore, appointed to develop a working classification of arterial diseases similar to the "Criteria of Diseases of the Heart" published by the American Heart Association (2).

The following classification (3) was presented at the 1952 meeting:

A. Degenerative arteriopathies
   1. Atherosclerosis
   2. Medial arteriosclerosis
   3. Arterionecrosis:
      a) idiopathic or nonspecific
      b) cystic medionecrosis (Erdheim (4))
      c) toxic arterionecrosis

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[1] Members of 1st Committee, 1948: Dr. Nelson W. Barker, Mayo Clinic; Dr. G. Lyman Duff, McGill University; Dr. Albert S. Hyman, New York Medical College; Dr. Irvine H. Page, Cleveland Clinic; Dr. Joseph B. Wolffe, Chairman, Valley Forge Heart Institute and Hospital.

Members of 2nd Committee, 1948–1952: Dr. Barker; Dr. Arthur C. Corcoran, Cleveland Clinic; Dr. Duff; Dr. Howard B. Sprague, Harvard Medical School; Dr. Wolffe, Chairman.

B. Productive and/or hyperplastic arteriopathies
C. Inflammatory arteriopathies
Arteritis. The following causes have been suggested:
a) infection
b) hypersensitivity
c) chemical
d) physical reaction to light, thermic conditions, roentgen rays and atomic radiation
e) trauma of mechanical origin.
f) undetermined origin
1) thromboangiitis obliterans (Buerger's disease)
2) cranial arteritis (temporal arteritis)
D. Combined forms of arteriopathies

The Committee arrived at the preceding tentative classification, after four years of study and frequent consultations with outstanding students of the subject both here and abroad.

The following is my personal interpretation of the suggested classification from a clinical point of view.

A. DEGENERATIVE ARTERIOPATHIES

Under this classification are included diseases of the arteries in which there is a gradual impairment or deterioration of the cellular components of the vessel wall, ultimately leading to:

1. Atherosclerosis
2. Medial arteriosclerosis
3. Arterionecrosis.

1. *Atherosclerosis*

Of these three, atherosclerosis is the most common variety of arteriopathy seen during and after middle life. Atherosclerosis, not heart disease, is the leading cause of physical and mental incapacities or death in our country. The process apparently is one of faulty local and/or general metabolism, in which the intima becomes the site of atheroma formation characterized by deposition of foam cells, cholesterol and cholesterol esters; it is healed by deposition of calcium. This arteriopathy seems to be associated with a number of factors, the chief of which are a) heredity—constitution, b) mode of life—high caloric food intake (rich in animal fat) in excess of expenditure of muscle energy, c) endocrine dysfunction, mainly of the pancreas with or without diabetes and lipemia, thyroid deficiency, and some gonadal and pituitary disorders, d) familial hypercholesterolemia and xanthelasma, and e) ? administration of ACTH and cortisone in certain experimental animals.

Diagnosis. The clinical recognition of atheromatous disease is not difficult in most instances. The following diagnostic criteria are of significance:

1. Family history suggestive of vascular accidents, diabetes mellitus and xanthelasma.

2. Personal profile pattern—pale complexion, sedentary occupation (usually overweight), tendency to be somewhat explosive in behavior, exaggerated drive in spite of external appearance of complacency. Patients experience quantitative and qualitative dyspepsia, particularly when under tension. These symptoms are often attributed to gallbladder disease and many patients have abnormal roentgenologic findings in the gallbladder.

3. Soft, palpably enlarged liver, upon careful examination (5). At times the liver is tender and the patient may volunteer this information.

4. The condition of the retinal vessels in atheromatous disease is usually not revealing, except in the presence of degenerative retinopathy; the changes then resemble those seen in diabetes mellitus. The sugar tolerance curve, however, is normal.

5. Transitory and episodic glycosuria without hyperglycemia, which is not an uncommon occurrence.

6. The condition of the arteries of the lower extremities (posterior tibial and dorsalis pedis); they show either a discrepancy in pulsations or do not pulsate.

7. Blood chemistry studies. In some instances the cholesterol levels are high and there is a disturbance of the cholesterol-phospholipid ratio. The interrelations of the lipids may be more important than blood cholesterol values alone. This may explain the lack of correlation between the severity of the atheromatous process and the blood cholesterol level.

8. Roentgenographic examination. Roentgenograms of the carotid artery, and the thoracic and abdominal aortas are valuable in this disease because the healing phase is usually associated with deposition of calcium in characteristic patchy patterns. This may be noted even before obliterative vascular changes occur. The areas most commonly involved are the abdominal aorta just above the bifurcation, the thoracic aorta and the carotid sinus. Another roentgenographic sign of equal significance is a widening of the supracardiac shadow owing to uncoiling of the upper part of the thoracic aorta, with veiling which extends from the aortic knob to the pulmonic conus.

9. The clinical findings. These will depend upon the organ which is deprived of proper blood supply, *e.g.*, cerebral thrombosis, coronary thrombosis, dissecting aneurysm of the aorta, rupture of the aorta, aneurysm of the abdominal aorta, mesenteric thrombosis and thrombosis of other arteries.

Treatment of atherosclerosis. Treatment must necessarily begin with the consideration of the possible etiologic factors. The diet seems to be at fault in many patients and must be corrected. This applies also to lack of physical exercise.

Endocrine disturbances should be minimized by supplementary therapy. Certain drugs, such as iodine, have long been used. Recently choline, inositol, and pyridoxin have been used for their alleged influence on fat metabolism. Ether administered intravenously in a well buffered solution seems to offer encouraging clinical results even in the late sequelae. It must, however, be used cautiously.

For many years we have been interested in the use of various pancreatic extracts (6). In previous articles (7, 8) we reported the use of a polyextract

from this organ in the treatment of atherosclerosis and its complications, and have obtained favorable results from its prolonged administration. It has been particularly valuable when diabetes is a complicating factor. Like all other remedies in the treatment of this disease, complete evaluation is as yet impossible.

2. Medial atherosclerosis

This second variety of degenerative arteriopathy frequently seen in general practice is also known as Moenckeberg's sclerosis.

Small deposits of calcium appear early in the media of arteries. Usually these deposits make their first appearance in the pelvic vessels. The process involves the muscular arteries, mainly the femoral (lower two thirds), the tibial, the radial, the pelvic and the temporal vessels. The calcium is deposited in rings, giving an appearance which is sometimes termed as "corduroy." This variety of calcification is not symptom-producing unless complicated by atherosclerosis. The physician as well as the patient should be aware of it, since it may otherwise cause unnecessary concern.

3. Arterionecrosis

This third type of degenerative arteriopathy is difficult to diagnose clinically. There are idiopathic and cystic varieties, which may ultimately lead to dissecting aneurysm of the aorta or dilatation of the aorta. This condition may be suspected in youthful patients if the ascending aorta is found to be dilated, with progressive aortic insufficiency in the absence of rheumatic fever, syphilis and hypertension. It is seen associated with congenital abnormalities (9). Toxic arterionecrosis is attributable to toxic substances of various origin, *e.g.*, renal and chemical (10).

B. PRODUCTIVE AND/OR HYPERPLASTIC ARTERIOPATHIES

This category of arterial disease is definable from a histopathologic point of view by hyperplasia of the intima and/or media, with concomitant changes in the distribution of the elastic tissue. It is a phenomenon often associated with, or resulting from, increased arterial pressure in either the systemic or the lesser circulation. The occurrence of this type of vascular disease may be independent of an elevated blood pressure; it is therefore designated as productive and/or hyperplastic rather than hypertensive. The factors concerned in hyperplastic and hypertensive disease of the arteries are so interwoven that, from a clinical point of view and in the present state of our knowledge, they could be considered as cause and effect.

In coarctation of the aorta, when the kidneys do not show effects of high pressure, the renal vessels are normal, whereas the retinal vessels show hyperplastic changes. It is, therefore, important that excessive high blood pressure be lowered by any safe available means.

We are not sufficiently aware that mitral stenotic lesions which cause increased pressure in the lesser circulation are responsible for hyperplastic pulmonary arteriopathies. The extent of the pulmonary hypertension can be determined clinically by the intensity of the second pulmonic sound, and by the results

of an electrocardiogram in addition to roentgenologic examination of the pulmonary artery. In such cases hemoptysis should be expected as a result of vascular rupture (pulmonary apoplexy), a condition which leads to relief of symptoms and should not be viewed with alarm. Mitral commissurotomy may prove a life-saving measure in suitable cases.

It is of paramount importance that the cause of hypertension be established in this group of arteriopathies. Idiopathic (essential), benign, and malignant hypertensions are well recognized as clinical entities. Methonium compounds hold out promise in the management as "medical sympathectomies" (11–13). Pheochromocytoma, usually in the adrenal or in the chromaffin bodies, causes at first paroxysmal, and later, sustained but fluctuating hypertension. Arterial hypertensive symptoms predominate, perhaps owing to the liberation of a pressor substance from the tumor. During crisis, hypertensive vascular retinopathy, hyperhidrosis, postural tachycardia, fever, increased basal metabolism, elevated fasting blood sugar, reduced dextrose tolerance and increased cardiac output are fairly constant findings. Sympathicolytic agents, such as benzodioxane, inhibit these manifestations, whereas histamine provokes the pressor crisis. Removal of the tumor effects a cure in most of these cases.

The hyperplastic arteriopathy of senescence, which is due to fibrosis of the intima and media with thickening and elongation of the vessel, is in itself not symptom-producing unless found in combination with some of the other forms of arteriopathy.

Bacterial toxins may at times affect the vascular wall, causing various hyperplastic arterial lesions (14).

In every case of hypertension it is imperative to establish possible etiologic factors. Only by attacking the underlying cause, can we hope to eliminate or reduce hypertension.

The type of hypertension encountered in acromegaly and Cushing's syndrome may be due to adrenal dysfunction (15). These patients, as well as those treated for Addison's disease with desoxycorticosterone without restriction of sodium chloride intake, are subject to rapid congestive cardiac failure while the salt intake is in excess. The possibility of a unilateral ischemic kidney, as described by Goldblatt, should be kept in mind as a possible cause of hypertension. Surgical removal of the kidney is the best therapeutic approach.

C. INFLAMMATORY ARTERIOPATHIES

Under this grouping (arteritis) are included inflammatory lesions of the arteries due to infection, hypersensitivity, chemicals, physical reaction to light, thermic conditions, roentgen rays, trauma and undetermined factors.

a) Arteritis due to *infection* is well known to the clinician. Primary arteritis is at times demonstrable in conditions such as influenza, pneumonia, typhoid and scarlet fever. Treatment in these cases is based upon proper bacteriologic diagnosis and a choice of suitable antibiotic agents.

b) Arteritis due to *hypersensitivity* (allergy) is more common than is usually realized.

In recent years periarteritis nodosa (polyarteritis nodosa, necrotizing arteritis,

panarteritis) has been considered by many to be due to an arterial hypersensitivity to some soluble foreign substances. Gruber (16) was the first one to recognize that periarteritis nodosa is a reaction to an organism to which the subject has become sensitized. He considered streptococcus protein as causative but recognized that other proteins might serve as the sensitizing allergens. Gruber's hypothesis was supported by Sigmund's animal experiments (17). Duff and Boyd (18) pointed out that sulphonamides alone may produce such reaction in man, supposedly by combining with plasma protein to make the antigen. Coincident asthma and eosinophilia which have been found in some of these cases strengthened the allergic theory as a causative factor in the production of periarteritis.

Due to the widespread distribution of the vascular lesions, the symptomatology is varied. The most symptom-producing lesions are those of the kidneys, skeletal muscles, skin, heart and brain.

Periarteritis nodosa has many remissions and exacerbations. The outstanding characteristic is the variability of the clinical picture. The physician should be aware of the possibility of periarteritis nodosa whenever he encounters a patient who has sepsis and presents a variety of widely spread symptoms and signs of a vague nature.

In a patient with a suggestive history and findings, a biopsy of any accessible lesion such as the skin, subcutaneous tissue or lymph gland is advisable, since it may be the only way of actually confirming the diagnosis of this disease during life.

The treatment is still questionable. Some improvement has been reported following the use of para-aminobenzoic acid. In some patients ACTH has decreased asthmatic symptoms; in others, there was prompt relief from cortisone.

c) The chemical form of arteritis is frequently seen among employees of chemical companies. Various substances are responsible; for instance, Chloroprene, an industrial chemical, is one of the causes of arteritis with coronary and hepatic manifestations. Experimental animal work with Chloroprene has shown arteritis involving the aorta and the vessels of the liver and kidneys.

d) Arteritis as a physical reaction to light and thermic conditions is seen following frost bite, foot emersion, roentgen rays and atomic radiation. These types of arteriopathy have received particular attention in military medicine, and medical literature readily available to every physician is full of pertinent facts as to diagnosis and treatment.

e) Trauma as a cause of arteritis should not be limited to mechanical injury alone. One can easily conceive that environmental impacts may gain expression through a component of the autonomic nervous system, producing an arteriopathy ("psychogenic angiothrombosis") (1). Careful questioning of the patient will make one suspect the possible existence of such an arteriopathy. Some forms of Raynaud's phenomenon may be included in this category, whereas others will fit into the following category.

f) Arteritis of undetermined origin is encountered in thromboangiitis obliterans (Buerger's disease) and cranial arteritis (temporal arteritis).

i) Thromboangiitis obliterans (Buerger's disease) is a variety of obstructive peripheral vascular disease in which both arteries and veins are involved. It first makes its appearance in the legs (19, 20). The early symptoms are feelings of heaviness, weakness and paresthesia in the legs. Swelling due to increased venous pressure, ulcers, and gangrene may appear early between the toes. This disease is undoubtedly aggravated or even caused by nicotine, and smoking is one of the first things to be discontinued. Therapeutic measures should be directed against the development of further interference with the peripheral circulation, and attention must be paid to the improvement of collateral circulation. Increased demands on arterial blood supply must be prevented. Trauma and infection of the afflicted areas should be avoided because of the subsequent greater demand for blood supply, and possible venous thrombosis. Active and passive vascular exercise, in addition to intravenous administration of saline and citrate solutions, seem to be of value in retarding progression of the disease.

ii) Cranial arteritis (temporal arteritis) usually starts with generalized malaise and pain in the ear and temporal region. Later on, the patients are febrile, and have anorexia with marked loss in weight. The arteritis may occur either unilaterally or bilaterally. It is ordinarily found in elderly persons, especially women. The etiology is unknown. The involved artery becomes inflamed, tender, tortuous and thickened. Pulsation may be absent owing to thrombosis. This arteriopathy was first described by Jonathan Hutchinson in 1890.

It is probably an infectious granulomatous disease resulting from localized pyogenic or mycotic infection or extension of infection of the teeth, sinuses or pharynx. Other arteries throughout the body may be similarly affected. Symptoms of generalized cerebral involvement such as epilepsy, papilledema, loss of hearing, diplopia, partial or total blindness and disorientation have been reported in literature (21).

No specific treatment is recommended, since the etiology is unknown. However, dramatic improvement has been reported following surgery. By removing a section of the involved vessel and dividing the regional sympathetic fibers, it is believed that extension of the inflammatory process to the vessels of the optic nerve and retina can be prevented (22). A therapeutic test of perivascular infiltration with 1 per cent procaine should be made before attempting to remove a section of the involved vessel (23). Cortisone has also been used successfully in cranial arteritis (24) and clinical improvement has been obtained with aureomycin when blood cultures showed Gram-positive cocci (25).

D. COMBINED FORMS OF ARTERIOPATHIES

As one would expect, the combined forms of any of the aforementioned arteriopathies are prevalent in the older age group. It is, however, important to determine which type is mainly responsible for the patient's symptoms. The

physician can then be of better service and keep pace with the rapidly advancing knowledge of medicine.

SUMMARY

1. The tentative classification of arteriopathies as presented by the Nomenclature Committee of the American Society for the Study of Arteriosclerosis at the annual meeting of the Society in Chicago in November 1952 is discussed from a clinical point of view.

2. The generic concept of arteriosclerosis is no longer acceptable, since it lacks specificity. Many types of arteriopathies are clinically distinguishable and yield to specific treatment.

3. The most common types of arteriopathies are discussed.

4. Differential diagnosis and treatment are suggested.

5. Arteriopathies, not heart disease, are the major cause of deaths in the United States of America.

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CORONARY ARTERY DISEASE IN THE AGED*

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I shall avoid three common types of introductory remarks in discussions of heart disease in the aged.

First, it would be presumptive of me to belabor this group with evidence, statistical or other, to indicate the importance of geriatrics. Second, the great frequency of heart disease and the increase in frequency with advancing age does not require further emphasis. Third, I shall not attempt to delimit any particular age group which constitutes the province of geriatrics. Clinical experience suggests that physiologic age is more important than chronologic age, and that the correlation between the two is poor. Furthermore, aging of various organ systems may not be parallel. The circulatory system, the skeletal system, the nervous system, or the respiratory system may age prematurely, for example, and thus the picture of physiologic aging may be variable. The nature, as well as the extent, of physiologic aging modifies the diagnostic as well as the therapeutic problems in the care of patients with arteriosclerotic heart disease.

Coronary artery disease results from coronary arteriosclerosis in the great majority of cases at all ages. Other etiologic factors are relatively unimportant. The frequency of other causes (such as rheumatism and syphilis) in the production of disease of the coronary arteries decreases after middle life, while the frequency of coronary arteriosclerosis increases, so that in the aged, coronary arteriosclerosis and coronary disease are practically synonymous.

In spite of the differences which age introduces in coronary artery disease, the similarities in different age groups are strong. Myocardial infarction at age 30, for example, presents a clinical problem which is very similar to myocardial infarction at age 80. These similarities, resulting from the common underlying pathologic condition, are much greater than the differences which follow from the effects of the aging process. I shall not undertake to give a general discussion of coronary artery disease, however, but shall attempt to stress some of the special problems in the management of the disease which are encountered in the aged.

First, the question of diagnosis is of interest. The differentiation from other diseases presents similar problems at all ages. Although the age of the patient modifies the relative frequency of diseases which are likely to be confused with coronary disease, the diagnostic methods employed do not differ greatly. Diagnosis must, however, go beyond differentiation of this disease from others pro-

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ducing similar symptoms. The manifestations are variable at all ages. No entirely satisfactory classification exists, but the one outlined here is helpful:

1. *Coronary arteriosclerosis without myocardial ischemia*
   a. Presymptomatic phase
   b. "Compensated" phase
2. *Coronary arteriosclerosis with myocardial ischemia*
   a. Coronary insufficiency (anginal syndrome)
   b. Myocardial infarction
   c. Cardiac insufficiency

All of the deleterious effects of arteriosclerosis of the coronary arteries are the result of myocardial ischemia. Arteriosclerosis which does not produce significant ischemia does not produce symptoms. Therefore, it seems useful to divide patients into two groups according to the presence or absence of significant ischemia. Patients without ischemia are subdivided into two groups, referred to as those in the presymptomatic phase and those in the compensated phase. The first group includes patients with coronary arteriosclerosis who show no clinical evidence of its presence. Those in the compensated phase include patients who have shown evidence of myocardial ischemia but have recovered.

Clinical identification of the presymptomatic phase is extremely unsatisfactory. Before ischemia, no definite evidence of the sclerotic process is available. This period is, however, of great importance, because stresses of various types are likely to produce acute manifestations of ischemia which could have been avoided. This problem becomes of greater significance as age advances and the incidence of sclerosis rises. It is desirable in advising individuals past the age of 60 or 65 about undertaking stressful situations, such as increased physical activity or surgery, for the physician to assume that coronary arteriosclerosis is present. The decision regarding the exact age at which this assumption is to be made is modified by the longevity of the ancestors and the frequency of arteriosclerosis among blood relations. There is not sufficient evidence to show that the level of any of the blood lipid fractions is important in making this estimate, particularly in the aged. The relationship between blood lipid aberrations and arteriosclerosis is most pronounced in the younger group, and even then is not sufficiently close to be of great help clinically. The frequency of this presymptomatic phase of coronary arteriosclerosis increases greatly in the aged. Since it cannot be identified with reasonable precision, it hangs, like the sword of Damocles, over the heads of all elderly persons and modifies not only their medical case, but their entire lives. The care of all elderly patients would be greatly improved if a precise means of identifying coronary sclerosis were available.

The compensated phase requires little special comment. The elderly, like younger patients, may recover from acute and chronic manifestations of coronary arteriosclerosis and remain free of symptoms for many years. It is certain that

coronary circulation may improve. Patients often recover from symptoms of chronic insufficiency of coronary flow. Recovery may occur, when angina is present, by the formation of an infarct with destruction of the ischemic tissue which gave rise to the angina; it may occur through the formation of adequate collateral circulation from dilatation of microscopic collateral channels and probably it may occur by actual regression of atherosclerotic lesions. Atherosclerosis has been clearly shown to be reversible in experimental animals under certain circumstances, although evidence in the human is not conclusive.

The classification of those patients who show evidence of myocardial ischemia is particularly unsatisfactory. Actually all of them suffer from coronary insufficiency, but we shall reserve that term for those without infarction or heart failure. The group with coronary insufficiency includes those with the anginal syndrome, the coronary failure cases of Blumgart and Freedberg and the acute coronary insufficiency of Master and co-workers. The latter attacks are characterized by pain of longer duration than the usual angina of effort, though they are unaccompanied by evidence of tissue destruction. They are often precipitated by extracardiac factors causing stress, such as emotion, exertion, fever, anemia, and exposure to cold or excessive heat; but they may occur without obvious stress, presumably because of reduction of the caliber of a coronary artery. This group of patients with coronary insufficiency without prolonged electrocardiographic changes, fever, leucocytosis and elevation of the sedimentation rate, has a higher average age than the group of patients with myocardial infarction. The problem occurs frequently among the aged and is of considerable importance, because the principles of treatment are different than in myocardial infarction. Treatment is directed to the relief and prevention of pain. If this can be accomplished, the period of inactivity can be shortened as compared with myocardial infarction. If relief of pain cannot be accomplished, however, the period of disability must be prolonged, for these people with frequent long attacks of coronary pain are highly susceptible to myocardial infarction.

Myocardial infarction occurs, of course, in the aged, but the classic attack is not seen as regularly as at earlier ages. Coronary insufficiency is relatively more frequent, and many of the infarction patients have atypical signs. It has been shown that so-called subendocardial necrosis is more common in the aged. In this condition, the symptoms may be indistinguishable from those of acute coronary insufficiency without destruction of tissue; but electrocardiographic changes, which are quite different from typical infarction patterns develop slowly. Low-grade fever and leucocytosis may appear after several days. This picture results from diffuse destruction of tissue in the deeper layers of the myocardium, without an obvious fresh thrombosis. The therapeutic problem here is similar to that in classic infarction, but the differentiation of this group from the group with acute coronary insufficiency is difficult.

It is clear that patients of advanced age with coronary pain require careful study and more than usual attention to the identification of the specific type of morbid process underlying the symptoms.

Cardiac insufficiency (congestive heart failure) requires emphasis. It is very frequent as a manifestation of coronary sclerosis in the aged. It is often seen in patients with angina, infarction, and other types of coronary insufficiency pain, but it may develop, usually gradually, without any pain. This painless coronary disease, manifested only by cardiac insufficiency, is particularly frequent in the aged.

The outstanding difference in this disease in the aged, then, is a great increase in the relative frequency of atypical clinical pictures. Although classic angina of effort and myocardial infarction do occur, cardiac insufficiency, acute coronary insufficiency and atypical myocardial infarction are more common. The incidence of coronary arteriosclerosis is extremely high, even in those patients who are entirely free of symptoms.

Time does not permit a detailed discussion of the great influence of various noncardiac diseases on the problem of coronary disease in the old age group. The frequent coincidence of emphysema, prostatism, renal insufficiency, cerebral vascular disease, carcinoma, malnutrition, diabetes, and other diseases changes the therapeutic problems considerably. The presence of hypertension, on the other hand, is a much less serious complication than in the younger age groups. Hypertension in the aged is usually benign, and has relatively little effect on the prognosis of coronary artery disease.

Attention should be drawn to the precarious situation of these patients with respect to fluid and electrolyte homeostasis. The use of parenteral fluids, low-salt diets and mercurial diuretics must be undertaken with great care, for the various mechanisms which maintain body hydration, intra- and extracellular electrolyte concentrations, and acid-base equilibrium become much less effective as age advances. The therapist, therefore, has a greatly increased responsibility in maintaining these equilibria.

With some trepidation, I have decided to close with a word regarding the psychologic problems in elderly patients with coronary artery disease. They differ somewhat from those seen in younger patients and, because of this, the objectives of treatment must frequently be modified. If the elderly patient has a real zest for living and if he is physiologically young, he should be given every advantage of careful treatment, regardless of his chronologic age. However, if he is depressed and resentful about old age in general and his disease in particular, and if he is uncooperative and careless in carrying out therapeutic recommendations, it is not helpful to use more than gentle suasion in an effort to persuade him to follow a regular schedule of medication, a dietary regimen, or activity restriction. It is not uncommon for vigorous efforts in this direction by physician, nurse, or relatives to intensify the depression or even to produce a psychosis. This, to me, represents a most difficult problem. It must be recognized that one must frequently settle for limited therapeutic objectives. On the other hand, one must avoid carelessness, for many oldsters can cooperate with, and benefit from, demanding therapeutic schedules. The estimation of the individual personality is difficult but important.

BIOPSY AND CYTOLOGIC DIAGNOSIS OF CANCER*

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BIOPSY DIAGNOSIS

The modern conception of the principle upon which the surgical cure of cancer depends is an operation in which the line of excision everywhere passes outside of the cancer and its local lymphatic metastases and through healthy uninvolved tissues. If this can be accomplished without killing the patient and there are no distant blood-borne metastases, a cure is assured. In these days of widely extended horizons in radical surgery, an attempt at radical surgical cure may mean functional loss, mutilation, and sometimes operative death. If the lesion is cancer, these are justifiable hazards; but if it is not, or if it is a form of malignant neoplasm which can be better treated by radiotherapy, such radical surgery will be a tragic mistake.

Although it is not infallible, the microscopic examination of tissue removed from the lesion is the most reliable method of diagnosis available and, whenever possible, a biopsy should be used to establish the diagnosis before therapy is undertaken. Probably the majority of surgeons will agree with this statement, but it is certain that a large minority do not, so that the thesis will be worth further discussion. I knew two excellent surgeons, both of whom are no longer living. They were keen diagnosticians and, in the case of breast lesions, sometimes preferred to rely on the clinical diagnosis, and forego a biopsy or disregard it. This led each of them into error. One of them repeatedly performed a local excision of a carcinoma because he supposed it was a benign tumor. The other several times undertook a radical mastectomy for benign lesions, the physical signs of which simulated those of carcinoma. Either no biopsy was performed or, if a frozen section was examined but failed to confirm his clinical diagnosis, he preferred to disregard the pathologist and proceed with the radical mastectomy. In my opinion both of these men committed avoidable errors which were either harmful, or at least not in the best interests of their patients. The harm was not great, for the first surgeon always had the supposed breast masses examined and as soon as he learned the lesion was cancer, proceeded to perform a radical mastectomy after a few days. Statistically such delay does not seem harmful, but theoretically it increases the hazards of metastasis. In the second case the undesirability of an unnecessary radical mastectomy is obvious.

Since lack of time will prevent discussion of all of the ways in which biopsy with or without quick frozen section can be of aid in the diagnosis and treatment of cancer, only a few of the more recently introduced procedures will be

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selected. It is hardly necessary to emphasize the importance of the biopsy in confirming the diagnosis of carcinoma of the breast before therapy. Recently R. S. Handley has called attention to the frequency with which cells from breast carcinomas metastasize to the internal mammary group of nodes. In our opinion at the Presbyterian and the Francis Delafield Hospitals, involvement of the internal mammary nodes makes the case incurable by operation, in spite of the efforts of Wangensteen and of Urban to extend the radical operation to include these nodes. Consequently, Haagensen has introduced biopsy of the internal mammary nodes with quick frozen section at the time of operation. If the findings are positive, the case is considered inoperable. This procedure follows, and is in addition to, frozen-section diagnosis of the breast tumor.

The importance of the biopsy in tumors of the soft tissues of the extremities and elsewhere should be emphasized. These tumors, both benign and malignant, are not common. Seemingly as a result of habitual and thoughtless practice, most surgeons simply excise them without appreciating that, if they are malignant, they always infiltrate insidiously well beyond their palpable confines, so that local recurrence is the rule and all too often is followed by lung metastasis and death. It is incomprehensible why surgeons will not adopt the same approach to these tumors that they do for carcinomas of the breast and gastro-intestinal tract, namely, first biopsy and confirmation of the diagnosis and then treatment based upon a knowledge of how these tumors spread and metastasize. Outside of a few large centers where the importance of this rational approach is appreciated, tumors of the soft tissues undoubtedly are the most unintelligently, and hence the worst, treated of all malignant tumors.

Surgery fails to cure carcinoma of the prostate, very largely because the carcinoma has seldom been recognized in living males when it is still confined within the prostate. An attempt is being made at the Francis Delafield Hospital to find occult cancers confined to the prostate when there is little or no clinical evidence of their presence. The undertaking is under the direction of Dr. Perry Hudson and the investigative procedure is carried out by incisional exposure of the posterior lobe of the prostate through the perineum, removal of a very generous slice of tissue from it and immediate examination by means of quick-frozen section. If localized occult carcinoma is recognized, an immediate total perineal prostatectomy is carried out. In this way it is hoped some carcinomas will be completely removed and cured before they have had a chance to spread. If no cancer is found, the incision, which can be made under local anaesthesia, is closed and no harm has accrued. We believe that punch or needle biopsies usually fail to detect the small occult carcinomas, and also possibly facilitate spread of the cancer by transplantation of cancer cells along the path of the needle.

These three examples will serve to illustrate the principle of biopsy for primary tumor diagnosis. In my opinion the incisional biopsy is always to be preferred to the needle or aspiration biopsy, if it is feasible; it should be as generous as possible because of the additional information which the larger biopsy specimen permits. For example, a tiny fragment broken from the surface of a projecting bladder tumor may permit a diagnosis of epithelioma, but it will not enable one to determine whether or not the bladder wall is infiltrated.

It is of great importance to have this information, because bladder cancers which infiltrate are very much more malignant than those which do not, and demand much more radical treatment if cure is to be attempted by surgery.

In a few instances, if a lesion is small, easily accessible, and the tissues in which it grows can be sacrificed with relative impunity, a biopsy excision may be justifiable. In this procedure the lesion is treated as if it were known to be malignant, and a wide zone of uninvolved tissue completely surrounding the lesion on all sides and in the depths, is removed with it.

Is biopsy a hazardous procedure? As far as can be ascertained, the three possible untoward effects are: 1) spread of a malignant tumor, either by local transplantation of cells or by facilitating metastases through lymphatics or blood vessels, 2) hemorrhage, and 3) perforation of the hollow viscera. By the exercise of due precautions in making the incision, providing for a dry wound, and treating instruments contaminated with tumor cells as if they were contaminated with bacteria, the probability of spreading tumor by biopsy is reduced to a minimum. No one can deny the possibility of spread; on the other hand, when such studies have been made, it cannot be demonstrated statistically that tumors from which biopsy specimens have been taken have a lower rate of cure or a higher rate of metastasis than those which have been left intact preoperatively. Serious hemorrhage or catastrophic effects from perforation of viscera so seldom occur that one may consider them remote calculable risks. The importance of the knowledge gained from biopsy so far outweighs its hazards as to make it a mandatory diagnostic procedure.

How reliable is it? It must be admitted at once that it is not 100 per cent reliable and, in my opinion, never will be. It depends upon the interpretation of certain phenomena by a human mind, and no human is infallible. Errors are made occasionally, even by the keenest and most experienced pathologist. The only question is, are they sufficiently frequent and sufficiently important to lead the cancer therapist into too frequent errors of commission and omission. With paraffin sections the error is only a fraction of 1 per cent. At the hospitals with which I am connected, frozen-section errors vary from 1 to 2 per cent. We try to guard against unjustified radical treatment by refusing to make a positive diagnosis if there is any doubt, and by repeating the biopsy more than once if doubt remains after the biopsy findings are reported as negative or equivocal. For example, when dealing with suspicious lumps in the breast, an attempt is made to give a positive diagnosis of either the presence or absence of carcinoma, by quick-frozen section. If diagnosis is impossible, the operation is terminated and nothing further is done pending the examination of the permanent paraffin section, which is easier to interpret. If an unequivocal diagnosis of a benign lesion is made by quick-frozen section and the lesion is excised, rarely an unsuspected carcinoma is found when permanent paraffin sections are prepared. Fortunately, the error can be corrected by a delayed radical operation without decreasing the statistical chances of cure. Thus, almost the only serious error which may be made is to call a benign lesion, carcinoma. For a pathologist who has had some experience with frozen-section diagnosis, this will be a very rare event.

Biopsy has many other uses beside primary diagnosis of tumors. The frozen section is used if, during an operation, the surgeon encounters what he fears may be unexpected spread or metastasis. For example, if a nodule is found in the liver during an operation on the gastro-intestinal tract, the operative procedure may be changed, depending upon whether or not the nodule is a metastasis. Nodules in the liver are by no means always metastases, so that frozen-section investigation is well worth while. Again, if an exenteration of the pelvis is contemplated and enlarged nodes are found above the pelvic brim, the attempt will probably be abandoned if these nodes contain metastatic cancer. These two examples have been chosen at random, merely to illustrate the fact that biopsy has endless uses in oncology beside that of diagnosis of primary tumors.

The diagnostic biopsy is one of the essential links in the chain of diagnostic procedures and, although not infallible, is probably the strongest and most reliable link in that chain. It should be emphasized, however, that the interpreter of the biopsy is neither a robot nor a magician, but a human being. If he is intelligent, well trained and experienced, possibly he knows as much, if not more, about the biologic behavior of the tumor in question than the average clinician because he encounters all of the tumors treated in his hospital, whereas the individual clinician is apt to be familiar only with his own cases. In hospitals with well developed tumor clinics this broader experience of the pathologist is recognized and made use of, but this practice is far from universal. A biopsy specimen may be sent to the laboratory with nothing more than a name attached to it, as if it were a specimen of urine. No wonder errors are made under such circumstances both by the pathologist and the surgeon, and inevitably it is in these hospitals that cancer is worst treated. The best treatment can be found only where there is harmonious cooperation between pathologist and oncologic therapist.

CYTOLOGIC DIAGNOSIS

The second method of tumor diagnosis which will be discussed concerns the collection and microscopic examination of secretions and excretions from various body orifices and internal surfaces, with the hope of finding in them desquamated tumor cells as isolated units or in small clusters. As is well known, this method, although not actually originated by him, has been brought to a highly developed state by George Papanicolaou and his disciples and followers. It has been used for two main purposes: 1) diagnosis, when the presence of a tumor is already known or suspected, and 2) as a technique for screening large groups of apparently normal individuals for the purpose of detecting the presence of unsuspected cancer in the hope that it will be in a curable stage. This second use of the Papanicolaou technique, especially in relation to the uterus and its cervix, has already been in use for some years in cancer detection clinics and by many gynecologists, so that it has become a problem of national importance. Its exact value is now a subject of debate and investigation. The subject is far too complex for discussion in this communication. Therefore, only the use of the cytologic technique as a diagnostic method will be dealt with.

It seems important to stress the fact that one of the essential factors in cytologic diagnosis concerns the way in which the material is obtained and is treated after it is obtained. Generally the material is useless for diagnostic purposes unless it is properly processed. This means there must be complete understanding and cooperation between those who obtain the specimen, those who are responsible for its transportation to the laboratory, and the laboratory workers who prepare and examine it.

It is also important to stress the fact that cytologic diagnosis differs from ordinary biopsy diagnosis by depending chiefly upon morphologic and tinctorial changes within single cells desquamated into a fluid, in which they are removed from their relationships with one another and with the supportive tissues in which they were growing. There are a whole set of criteria which differentiate these cancer cells from noncancerous cells that may have been desquamated with them, and the cyto-pathologist must learn these criteria if he expects to make accurate diagnoses. Therefore it must not be assumed that a pathologist is *ipso facto* a cytologic diagnostician. He will not qualify as one, unless and until he has had both training and experience.

Cytologic diagnosis generally requires a great deal more time than biopsy diagnosis because desquamated tumor cells may be few and difficult to find in smears and fluids. If a laboratory is called upon to make many cytologic examinations, it becomes essential to train cytology technicians who process the material and, after staining it, search for abnormal cells which they have been trained to differentiate from normal cells. The pathologist is thus spared long hours of search through normal specimens and can concentrate on the slides with abnormal cells, which may or may not be cancerous. This, however, appreciably increases the cost of running the laboratory and thus raises economic as well as scientific problems.

It is necessary to realize all of these things so that no one shall suffer from the illusion that proper cytologic diagnosis is something that can be achieved merely by ordering its adoption. I feel confident that its most enthusiastic proponents will agree with me that much harm can result from false positive and false negative diagnoses, made because of insufficient training and experience.

In diagnosis, the method has greatest value when cancer cells can be found in secretions and excretions coming from suspected carcinomas which can be reached for biopsy only by major or undesirable operative procedures. In skilled hands it has proved accurate in cancers of the lung involving the bronchi, situated where they cannot be visualized or where a biopsy cannot be performed through the bronchoscope, and when the roentgen diagnosis is equivocal. Cancer cells may be found in the sputum or in bronchial washings. Unfortunately, positive findings have probably done little to improve the cure rate for lung cancer, because all too frequently when the diagnosis is made, the carcinoma is already incurable.

Unquestionably the method has its widest application in cancer of the cervix and of the corpus uteri, both suspected and unsuspected. In a good many clinics it is now used as a routine part of a physical examination. Positive or equivocal

results have led to the discovery of unsuspected cancers, including both the infiltrative and the *in situ* varieties, as well as an occasional corpus carcinoma. Everyone will agree that this is a brilliant achievement. In the best clinics, a positive or doubtful Papanicolaou smear is always checked by biopsy and often by curettage as well, if deemed necessary. It seems important, however, to stress a fact which has come to my attention, namely, that there are gynecologists who have performed pan-hysterectomies on the basis of a positive Papanicolaou smear alone. Evidently those who were interpreting the smears were insufficiently or improperly trained, for subsequent study of many of these specimens failed to show any neoplasm, either superficial or infiltrating. This is stated, not in criticism of the method, which has a high degree of accuracy in experienced and well trained hands, but to emphasize its dangers when improperly applied. The method is also useful in following patients after treatment, when looking for possible recurrences and in checking the reaction of the vaginal epithelium to radiation treatment.

There is little use for the method in the study of the bladder, which can be visualized and from which biopsy specimens can be obtained directly, but it has proved to be diagnostic if tumor cells are found in catheterized specimens of urine coming from one or the other of the kidneys.

In some clinics, in cases of suspected carcinoma of the prostate, it has been the practice to massage the prostate and examine the collected secretions for cancer cells, which have been found in a number of instances. This is a very questionable procedure for two reasons: 1) the massage of a cancer is hazardous because it increases the chance of spread by metastasis; and 2) if a cancer of the prostate is large enough to have grown into a position where its cells can be desquamated into its secretions, it is already almost certainly incurable by operation. In any event, the suspected case will be subjected to biopsy, which is safer and more accurate.

The same warning applies to manipulation of the nipples in order to obtain from mammary ducts the material which can be searched for tumor cells. Perhaps, if the manipulation be limited to the nipples, there is no danger of massaging a breast cancer, but if the practice were widely used there would be some examiners who inadvertently would massage the breast as well. Since discharge from the nipple is a very rare early sign of breast carcinoma, it seems unlikely that the method would succeed in revealing the presence of an unsuspected breast cancer except in the rarest instances.

There have been a number of attempts to detect the presence of tumor cells in gastric fluids. The direct examination of untreated gastric washings has been disappointing. Apparently cancer cells are not so easily desquamated from gastric cancer as from cancers in other sites, and the presence of gastric mucus interferes with locating the cells, if present. In order to deal with the mucus, it has been found that papain can be used as a mucosolvent without damaging cancer cells, and those who have tried the method report a greater degree of success than without it. Another procedure which is a cross between exfoliative cytology and biopsy is the abrasive balloon, devised by Cooper at the New York Hospital. This is an ingenious method of scraping the mucosal

surface of the stomach without causing important hemorrhage or injury, and Cooper, Papanicolaou and their co-workers report a high degree of diagnostic accuracy for it. They warn that there must be an unusual amount of close cooperation between all concerned in the procedure, if it is to be used with success.

One of the oldest uses of the cytologic method and one which antedates Papanicolaou's special staining techniques is the examination of fluids withdrawn from serous cavities. It is an important diagnostic procedure but with our present methods of therapy, if cancer cells are found, it will not lead to cures; for the involvement of peritoneum, pleura or pericardium by malignant tumors is a sign of incurability and the best that treatment can offer is palliation.

These examples do not exhaust the possible uses to which the method has been put. Material from the rectum, the nasal sinuses, the auditory apparatus draining sinuses or fistulae, the duodenum, the esophagus (when biopsy fails) indeed, from any tract with access to the body surface so that desquamated cells can be obtained—has been subjected to search for cancer cells. When found, the diagnostic information may be very helpful, although it requires many negative results to suggest that no cancer is present; it is never safe to reach that conclusion from cytologic examinations alone.

This discussion is an attempt to present the subject of diagnostic exfoliative cytology in an objective and nonpartisan manner, for a very good reason. Cytologic diagnosis is a relatively new technique. A relatively small number of pathologists and cytologists have become experts in interpretation, but a great many of those who are employing the technique are inadequately trained and without sufficient experience to qualify as reliable diagnosticians. In the forty years during which I have been studying and practicing tissue diagnosis a very great deal has been learned about tumors; yet no day goes by without my seeing something new. Inevitably, it will take more than three or four months' training to become a qualified cytologic diagnostician. Cytologic diagnosis is a legitimate diagnostic procedure, which will gradually become available in every laboratory of diagnostic pathology, but more should not be expected from it than it can give and confirmation should always be sought by biopsy if at all possible. The method is still under investigation and the report of a positive finding may not necessarily indicate infiltrative cancer.

SUMMARY

Biopsy is an essential and decisive step in tumor diagnosis and should be used freely in all cases in which it is practicable. Cytologic diagnosis should be used with caution and should be considered reliable only if interpreted by an expert. It should be confirmed by biopsy in all cases before curative therapy is undertaken. If the pathologist and cytopathologist are to be of most use in diagnosis and interpretation, they must be fully cognizant of all available clinical, roentgenologic and laboratory information; for tissue diagnosis must not only provide a label but must also predict the probable biologic behavior of the countless neoplasms and cellular hyperplasias.

BENIGN ULCER AND CARCINOMA OF THE STOMACH

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Gastric ulcer presents four important and difficult problems to the physician. The first is the possible malignant transformation of benign gastric ulcer and the frequency of such change. This question has been controversial. It is obvious that, if malignant change occurs frequently in benign ulcers, most patients with gastric ulcers should undergo surgery. If such transformation were extremely rare, it might be wise to treat more of these ulcers medically and avoid the operative mortality and morbidity coincident with gastric resection. Consequently, this problem is of paramount importance to the physician treating the patient with benign gastric ulcer.

The second question is whether a specific ulcer is benign or malignant. What are the criteria that are helpful in differentiating between these lesions, and how accurately can the differential diagnosis be made?

The third problem is the effectiveness of medical treatment of the patient with a benign gastric ulcer. If many of the patients are promptly and permanently relieved of their distress, medical therapy would be highly effective and advisable in the majority. If, on the other hand, a great number of patients with benign ulcers become gastric cripples and have repeated recurrences, medical therapy should be considered a failure and surgery should be recommended.

The fourth consideration is the effectiveness of surgical treatment. The postoperative mortality and morbidity rates, the late sequelae of gastric resection (such as the "dump" syndrome, weight loss, diarrhea and anemia) and the recurrence rate of jejunal ulcer following gastric resection for gastric ulcer, are all factors which must be considered and evaluated.

These four problems are important in deciding whether to treat a patient with an apparently benign gastric ulcer medically or surgically. It is desirable to operate on patients with gastric cancer as early as possible. It is distressing to have a patient with benign disease die postoperatively. That the proper advice be given is particularly important to the aged patient. Despite the growing audacity of many surgeons, the aged patient is an increased operative risk and also frequently shows an increased incidence of postoperative complications and morbidity. Concomitant diseases such as cardiovascular and renal disease, malnutrition, diabetes, cerebral changes and simple senility increase the risk of surgery in these patients. Consequently, if operations can be safely avoided, it is desirable to do so. The same associated diseases that trouble the surgeon may also handicap the internist in his treatment. The older patient may forget to take "anti-acid" when instructed, and may not be cooperative in following a medical program.

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The purpose of this paper is to evaluate these four problems, in order to determine whether patients with apparently benign gastric ulcer should have medical or surgical treatment.

I. MALIGNANT TRANSFORMATION OF BENIGN GASTIC ULCER

Whether or not benign gastric ulcers become malignant, and the frequency of such occurrences, have been controversial issues since Wilson and MacCarty (1) reported in 1909 that 71 per cent of gastric carcinomas arose from benign ulcer. The extreme difference of opinion is evident in comparing the previous percentages with a statement of Palmer (2) in 1939, that "The existence of carcinomatous degeneration in benign ulcer remains to be proved conclusively". Some of the literature has been previously reviewed by us (3). Waugh and Charendoff (4) reported 10 cases, among 263 gastric resections for cancer, in which they thought the neoplasms arose in benign gastric ulcers. Cain *et al.* (5) reported 34 cases of cancer in 414 patients with supposedly benign ulcers, in 11 of whom the neoplasm developed five or more years after the diagnosis of benign ulcer. Smith and Jordan (6) reported 2 of 111 patients with benign ulcer in whom gastric carcinoma developed from five to twenty-three years after the original diagnosis.

The author's experience will be briefly summarized. The pathologic findings in patients with gastric ulcer and carcinoma of the stomach who were subjected to surgery at the Cleveland Clinic from 1945 to 1951 have been reviewed (3). Criteria have been established for making a diagnosis of carcinoma arising in a benign gastric ulcer. In these cases, first it was necessary that there be definite evidence of a chronic peptic ulcer. This included the characteristic layers of peptic ulceration with a fibrinopurulent exudate, a zone of necrosis, granulation tissue, a dense fibrous base with loss of muscularis, and vascular changes such as thickening of the vessel wall and the formation of thrombi. Second, there had to be definite evidence of carcinoma. This included changes in the staining quality of the nuclei, changes in polarity, atypical mitotic figures, and infiltration of the neoplasm beneath the muscularis mucosa; the carcinoma began at the margin of the ulcer and was not desmoplastic.

There were only 8 cases that fulfilled all these requirements and were considered to be probable examples of carcinoma arising in benign gastric ulcer. During the same period, a clinical diagnosis of gastric ulcer was made in 715 patients, with an incidence of 1.1 per cent of gastric ulcers developing carcinoma. During the same period a clinical diagnosis of carcinoma of the stomach was made in 773 patients; 520 were operated upon and tissue diagnoses were obtained. With only 8 instances of carcinoma arising in benign ulcers in 520 cases of proved gastric carinoma, it is apparent that relatively few carcinomas developed from benign ulcers. Thus, in only 1.5 per cent of all patients subjected to surgery for carcinoma of the stomach, could it be shown that the cancer arose from a benign gastric ulcer. The previous figures indicate that, although gastric ulcer may undergo malignant change, it rarely does so, and the majority of carcinomas of the stomach do not arise from pre-existing gastric ulcers.

The clinical aspects of these 8 patients were interesting. The symptoms were typical of ulcer distress, only 2 of the 8 patients having experienced a recent change. The average duration of the symptoms was 3.7 years, whereas the average duration in patients with gastric carcinoma has been eleven months (7). The relatively long duration of symptoms is somewhat suggestive of a benign ulcer preceding the carcinoma. An epigastric mass was palpated in one patient. Three patients were anemic, but the results of gastric analyses were normal in all but one, who had a hyperchlorhydria. Four of the gastric lesions were in the antrum and pylorus (a common site for carcinoma of the stomach) and four were along the lesser curvature above the angle (a common site for benign ulcer).

We believe the foregoing data indicate that:

1. Benign gastric ulcer may undergo malignant change.
2. Such malignant transformation is rare (malignancy developed in only 1.1 per cent of the gastric ulcers).
3. The majority of gastric carcinomas (98.5 per cent) do not arise from pre-existing gastric ulcers, since in only 1.5 per cent could such a relationship be established.

II. DIFFERENTIATION OF BENIGN AND MALIGNANT ULCERS (FIGS. 1–4)

Cancer of the stomach occurs more frequently in the older age groups, and one must be particularly alert to the possibility of gastric cancer in elderly patients. Norbye (8) reported that the highest incidence of gastric ulcer in men was found in the ages from 40 to 50 years, and in women in the ages over 60 years. Benign gastric ulcer may occur at any age. Symptoms in the older groups may be atypical and may simulate cardiac disease or may exist concurrently with cardiac disease, so that the patient himself is unable to tell whether his distress originates in the stomach or in the heart. Similarly, the symptoms may mimic gallbladder and other gastro-intestinal diseases. Not infrequently the ulcer may be asymptomatic in the older person, or may manifest itself only by some complication such as hemorrhage or obstruction.

The differential diagnosis between benign and malignant ulcer may be most difficult, and a trial of medical therapy for three to six weeks may be necessary to aid in the diagnosis. There are a number of factors to be considered in any patient with a gastric ulcer.

The duration of symptoms is not of much assistance in the differential diagnosis. Collins *et al.* (9) found that the average duration in 100 cases of gastric ulcer was 4.7 years, and the average in our 8 patients with carcinoma arising in a gastric ulcer (3) was 3.7 years. The average duration of symptoms in our patients with carcinoma of the stomach (7) was eleven months. However, any person with a gastric ulcer may have a short symptom-history, whereas a patient with a gastric cancer may have had "indigestion" for years. The type of symptom is not particularly helpful. Anorexia and weight loss are commonly associated with malignancy, but are late symptoms which may also be present in the patient with benign gastric ulcer with obstruction.

A B C

FIG. 1. Slow healing of gastric ulcer. A. Large gastric ulcer near the cardia of the stomach, resembling a gastric diverticulum. That the lesion is benign is suggested by the smooth contour and sharp definition of the ulcer crater. Feb. 13, 1952.

B. Ulcer smaller after six weeks of intensive medical therapy. Mar. 28, 1952.

C. Only a trace of the ulcer remains after two and a half months of medical treatment. Usually if the ulcer is not healed completely in six weeks, surgery is recommended. However, this patient had very severe hepatic cirrhosis, contraindicating operation. Repeated x-ray examination of the stomach in the past eight months showed the ulcer to have healed completely and to have remained healed. April 25, 1952.

Gastric analysis usually contributes little. The ulcerating neoplasms frequently are associated with normal or increased acidity. If the patient has a histamine achlorhydria, however, the lesion should be considered malignant. If low, normal or increased acidity is found, gastric analysis is of no help in the differential diagnosis. The continued presence of occult blood in the stool suggests malignancy.

The location of the lesion is of considerable assistance. It was formerly believed that most of the antral lesions were neoplastic. Portis and Jaffe (10) reported that 59 per cent of benign ulcers were in the antrum (autopsy material—196 gastric ulcers). Smith and Jordan (6) found that 73 of 211 proved benign ulcers were in the antrum. However, Palmer (2) reported that Konjetzny found that 82 per cent of gastric carcinomas involved the antrum and that Graham concluded that 94 per cent of gastric ulcers distal to the incisura were malignant. The antrum is the most frequent site of neoplasm of the stomach, and we must be suspicious of any ulcerating lesion in this location.

Benign ulcers along the greater curvature are rare. It has been estimated that 95 to 98 per cent of the ulcerations in this location are malignant. Because of the high incidence of neoplasm, and regardless of the increasing number of reports of benign ulcer of the greater curvature, we believe that surgery is indicated for any such lesion.

Ulcerations along the lesser curvature above the angle or incisura are usually benign (90 per cent of the cases). It is easy to follow the course of these ulcers both roentgenologically (Figs. 3 and 4) and gastroscopically. Lesions in this area are the ones which we usually attempt to treat medically. Posterior wall ulcerations, particularly when near the lesser curvature, are also usually benign. Oblique roentgenograms will frequently demonstrate such ulcers satisfactorily. The closer a posterior wall ulcer is to the greater curvature, the greater the possibility of malignancy.

Fluoroscopic examination can be definitely helpful; lack of peristaltic activity and stiffening of the wall are suggestive of malignancy. Fluoroscopy should be carried out with both small and large amounts of barium. It is important to supplement fluoroscopy with films, including spot films and pressure technique. Proper positioning of the patient with oblique films may demonstrate a posterior wall ulcer not otherwise evident.

The appearance of the ulcer by roentgen examination is of great assistance in the differentiation (Figs. 1 and 2). Usually the greater the penetration of the ulcer, the greater the likelihood that the ulcer is benign. The size of the crater alone is of little help (7); it is frequently stated that ulcerations greater than 2.5 cm. are malignant. However, benign ulcers can be unusually large, and ulcerating neoplasms can be small. There is a tendency to recommend surgery for any ulcer greater than 2.5 cm. in size, not only because of the increased possibility of malignancy, but also because there is a great deal of fibrosis susceptible to recurrent ulceration with the healing of such a large ulcer.

The presence of a filling defect around the ulcer, or a subtraction defect, or the meniscus sign of Carman (a halo around the base of the ulcer) is suggestive

FIG. 2A

FIG. 2B

FIG. 3A

FIG. 3B

FIG. 4A

FIG. 4B

of neoplasm (Fig. 2). It has been pointed out that spasm and edema of a benign ulcer can simulate neoplasm in this manner; nonetheless, with the presence of any of the foregoing signs, we usually recommend surgery. The contour of the ulcer can also be of help in the diagnosis. If the contour is irregular with the edges not sharply defined, the ulcer must be considered malignant; if the ulcer is very sharply defined with a smooth contour it probably is benign (Fig. 1). The presence of spastic phenomena or an incisura on the greater curvature opposite an ulcer is suggestive of a benign lesion. Radiating folds to the ulcer crater also suggest that it is benign.

Ulcerating lesions higher in the stomach frequently cause considerable antral spasm. Such antral spasm should not be misinterpreted as carcinoma. With treatment of the ulcer higher in the stomach the antral spasm will usually disappear.

Gastroscopic examination is an aid in differentiating benign from malignant ulcer, and in observing the progress of healing. This type of examination is most useful in lesions above the angle, along the lesser curvature. Ulcers in the antrum and posterior wall frequently are in the "blind area" and may not be visible gastroscopically.

The progress of the patient during medical therapy is most important. He should be entirely asymptomatic in three weeks, and the ulcer crater should be smaller. By six weeks he should continue to be asymptomatic and the crater should have disappeared (Fig. 1). It is surprising how rapidly even an unusually large gastric ulcer can heal on adequate medical therapy. If the ulcer has not healed in six weeks, it should be considered malignant and surgery should be recommended.

It is important that the patient be followed even after the ulcer has healed. We usually recommend roentgen examination of the stomach every three months for the first year, and then yearly for some time thereafter. Recurrence of gastric ulcer is frequently an indication for surgery. Smith and Jordan (6) have stated that there is some indication that the recurrent ulcer or the long-standing untreated gastric ulcer is more likely to undergo carcinomatous change.

FIG. 2. A. Spot film of moderate sized benign gastric ulcer. The sharpness of the outline, the smooth contour, the lack of any filling defect and the depth of penetration all suggest a benign lesion.

B. Benign gastric ulcer near the cardia. The subtraction and filling defect proximal and distal to the ulcer crater suggests a malignant ulcer. At operation the ulcer was found to be benign, the apparent subtraction defect above and below the ulcer being due to edema and inflammation.

FIG. 3. A. Benign gastric ulcer on the lesser curvature. There is an apparent subtraction defect, but this is due to spasm. The presence of two incisura on the greater curvature opposite the ulcer suggests that the lesion is benign.

B. In six weeks the ulcer has completely healed under intensive medical treatment.

FIG. 4. A. Ulcerating gastric neoplasm on the lesser curvature, with extension proximally. The irregularity above the ulcer on the lesser curvature is indicative of extension of the neoplasm.

B. Extensive ulcerating neoplasm of the proximal half of the stomach. The irregularity of the ulcer and the presence of a subtraction defect indicate extensive ulcerating carcinoma.

By using the foregoing criteria, following the patient with frequent roentgen examinations of the stomach, operating upon questionable lesions (those which do not heal within six weeks) and on recurrent gastric ulcer, the diagnostic error can be kept within the range of operative mortality (1 to 2 per cent). The importance of adequate follow-up examinations cannot be overemphasized. If the patient cannot or will not return for progress studies and observation, surgery should be recommended. All the factors mentioned should be considered carefully for each individual patient.

III. THE EFFECTIVENESS OF MEDICAL THERAPY OF BENIGN GASTRIC ULCER

The effectiveness of medical treatment of gastric ulcer has been questioned in two recent reports. Flood and Hennig (11) reported that only 6 of 47 patients followed for five years had no recurrences. In 5 of the original 101 patients carcinoma developed two years or more after the diagnosis of benign gastric ulcer.

Cain *et al.* (5) of the Mayo Clinic reported 414 cases of benign gastric ulcer treated medically. Medical therapy was abandoned for surgery in 140 patients or 33.8 per cent. Only 85 patients or 20.5 per cent obtained complete relief on medical management. An additional 71 patients or 17.2 per cent had partial relief. It should be noted in their report that medical treatment was not carefully supervised and in most cases was not instituted at the Mayo Clinic. Many physicians may not understand what comprises *adequate medical therapy*. We have seen patients with active ulcers who have been told by their local doctors to take an "anti-acid" after meals, only when having distress, or only an hour after meals and at bedtime. Such treatment should not be considered adequate medical treatment, any more than gastro-enterostomy would be considered adequate surgical treatment. There is a tendency to consider any nonsurgical treatment as medical therapy, which is far from true. The Mayo Clinic may be handicapped in treating gastric ulcers medically, by the difficulty in obtaining the vital progress examinations (as outlined in Section II of this paper) on patients who live so far from the institution. Unless such progress studies can be obtained, surgery should be seriously considered. We agree with the authors that if medical therapy is no better than 20.5 per cent satisfactory, surgical intervention is indicated in a greater percentage of cases.

Other reports are more favorable. Judd and Priestley (12), also from the Mayo Clinic, reported a clinical cure in 46.5 per cent of 146 patients treated medically and followed for five to twelve years. An additional 15.8 per cent obtained satisfactory results if they continued to follow the medical treatment. Smith and Jordan (6) reported that the recurrence rate after five years in 111 patients was 46.8 per cent; in other words, 53.2 per cent had no recurrences. R. C. Brown (13), who followed 77 patients from three to eighteen years, found 41 per cent definitely cured and 20 per cent greatly improved.

Collins, La Tona, and Clark (9) obtained follow-up studies on 100 patients with gastric ulcers seen at the Cleveland Clinic. All patients were followed for a minimum of five years (the average being 7.1 years). Twenty-seven of the

100 were referred to surgery without a trial on medical therapy. Seventy-three patients were treated medically. Fifteen of the 73 patients were referred to surgery after only one to two months of medical treatment, because the ulcer did not heal promptly. Forty-three of the 73 patients initially treated medically made a satisfactory response. Thus, 59 per cent of the patients treated medically and followed for a minimum of five years and an average of 7.1 years responded to medical treatment. Forty-two patients were referred to surgery immediately, or within two months. Of the remaining 58 patients treated medically for more than two months, 43 patients (74 per cent) made a satisfactory response. These results of medical therapy are encouraging.

The success of medical treatment can also be determined by the number of patients who are referred for surgical treatment. At the Mayo Clinic, according to Cain *et al.* (5), partial gastrectomy is the treatment of choice in 60 to 70 per cent of the patients with gastric ulcer, and they believe that early surgical intervention is indicated in a higher percentage of patients. Smith and Jordan (6), reported 541 cases; 330 (60 per cent) were treated medically, and 211 were operated upon. Our own figures are somewhat lower; 38 per cent of our patients with gastric ulcer were operated upon in 1949 and 1950. The percentage of patients operated upon for gastric ulcer, however, has increased from 18 per cent in 1945 to the present figure.

It would seem from most of the published studies that an adequate medical program for benign gastric ulcer should result in at least 50 per cent of the patients having no recurrences for five years. In studies reporting 20 per cent or less of satisfactory results, the medical therapy must have been inadequate, with insufficient progress roentgen studies and observation. The basis of adequate medical therapy has been well outlined by R. C. Brown (14) in Oxford Medicine. Our treatment is similar to the treatment we have outlined for patients with duodenal ulcer (15), except that anticholinergic drugs are not employed in the therapy of gastric ulcer.

We believe that the results of *adequate medical therapy* are sufficiently favorable to warrant its continued use in benign gastric ulcer. This is particularly true of the elderly patient who is an increased operative risk. The growing conviction of surgeons that every gastric ulcer patient should be operated upon is deplorable. Although it is easier for the internist to shift the responsibility to the surgeon and avoid the necessity of periodic observation of the patient, this does not mean it is better for the patient. Each case must be considered individually. If the ulcer appears benign, if it heals promptly on adequate medical therapy, medical treatment should be continued and the patient should have periodic roentgen examination of the stomach.

IV. THE EFFECTIVENESS OF SURGICAL TREATMENT

There is considerable evidence to support the view that the most successful operation for gastric ulcer is gastric resection. This discussion is concerned only with this procedure. Vagotomy has no place in the treatment of gastric ulcer, in contrast to duodenal ulcer. Gastro-enterostomy alone has been found

unsatisfactory in the treatment of any peptic ulcer and has been generally discarded.

The operative mortality for gastric resection in the best centers usually is from 1 to 2 per cent, which certainly is not prohibitive. In hospitals where the trained resident staff, common in larger medical centers, is not available, the postoperative mortality will be somewhat higher. Antibiotics, better anesthesia, and improved preoperative and postoperative care have reduced the mortality to a satisfactory level. It is still distressing to lose 1 or 2 patients in 100 following surgery for benign disease. In the older age group, this mortality rate is higher.

It is generally recognized that few gastrojejunal ulcers or marginal ulcers develop after gastric resection for gastric ulcer. Walters and Clagett (16) followed 162 cases of gastric ulcer for from one to five years and found that in none of them had gastrojejunal ulcers or marginal ulcers developed after resection. Ransom (17) followed 188 patients who underwent gastric resection for gastric ulcer and found that in only 4 had marginal ulcers developed. Bjørneboe *et al.* (18) reported 44 patients, 3 of whom had recurrent pain, and 1 of whom also had hemorrhage. Brown and Hoerr (19) reported 1 case of marginal ulcer which developed following a Billroth I procedure for gastric ulcer.

Other complications follow gastric resection, however, that may make some of the patients extremely miserable and prove difficult to treat. Bjørneboe *et al.* (18) reported that 14 per cent of their patients were unfit for work. However, in only 44 of 189 patients was the resection for gastric ulcer; in 145 patients it was for duodenal ulcer. Appreciable anemia occurred in 4.3 per cent of their patients.

We have seen 2 patients who, after gastric resection, were persistently anemic with a hemoglobin below 10 Gm. Various therapies with massive oral doses of iron, liver extract, and vitamin B_{12} proved ineffective in raising the hemoglobin. Finally, intravenous iron was given, which promptly raised the hemoglobin above 12.5 Gm. One of the patients so treated maintained her hemoglobin above 12 Gm. for six months without any parenteral or oral therapy; whereas, prior to administration of iron intravenously, her hemoglobin had remained below 10 Gm. for over a year. It is not known whether or not the antrum of the stomach is a factor in iron absorption; but these 2 patients did not absorb enough iron when given in massive oral doses, although they did respond to iron given intravenously. We hope to study them further and perhaps report other patients who require intravenously administered iron following gastric resection.

We have 1 other patient who has had persistent vomiting once or twice a day since her gastric resection two years previously. Repeated roentgen examinations of the stomach and small bowel show no evidence of obstruction or of a gastrojejunal ulcer, and we have been unable to establish any cause for her vomiting. She has not responded to various types of medical treatment and continues to be a gastric cripple following her resection.

Some patients have considerable difficulty regaining weight following re-

section. Frequently their weight slowly decreases until it becomes stabilized at a new level. In about 5 per cent of the patients this malnutrition can be a serious problem. Following gastric resection, some patients are troubled with the "dump" syndrome and others develop diarrhea. The diarrhea can contribute to the malnutrition. Some patients are never able to eat as much postoperatively as they were prior to operation.

The fact that some patients present serious sequelae of gastric resection is evident from a review of the literature on the treatment of the "postgastrectomy syndrome." Various remedies have been recommended, including liver extract, a continued medical ulcer program, potassium salts before meals for the "dump" syndrome, a high-protein low-carbohydrate diet, anticholinergic drugs such as Banthine, cholinergic drugs such as urecholine, enterogastrone for postgastrectomy gastritis, and Sorlate to aid in absorption of fat. The ineffectiveness of these remedies is obvious from the number of different treatments that have been recommended for the "postgastrectomy syndrome." The problems (*e.g.*, malnutrition) of some of the patients following gastric resection caused Chester Jones (20) to postulate that the gastric antrum may possibly secrete a hormone important in intestinal absorption.

In general, the operative mortality for gastric resection is satisfactory. In not more than 1 to 2 per cent of the patients does a gastrojejunal ulcer develop. Other postgastrectomy sequelae such as persistant anemia (without a marginal ulcer), malnutrition, "dump" syndrome, and diarrhea are troublesome in about 10 per cent of the patients. These sequelae can present more difficult problems than the original ulcer, and can incapacitate some of the patients.

SUMMARY

A review of 773 cases of carcinoma and 715 cases of benign ulcer of the stomach indicates that, although gastric ulcer may undergo malignant change, this is a rare occurrence. The majority of carcinomas of the stomach do not arise from pre-existing ulcers. In only 1.1 per cent of the patients with gastric ulcers did malignancies develop; in only 1.5 per cent of the patients with gastric carcinoma operated upon, could we show that the carcinomas developed from benign ulcers.

The various factors to be considered in the differentiation between benign and malignant gastric ulcers are discussed. All evidence possible should be available to the physician making such a decision. Lesions along the greater curvature, certain ulcerations in the antrum, ulcers associated with a histamine achlorhydria, ulcers with a meniscus sign or with irregular craters or associated with a filling defect, those associated with persistent blood in the stool, and those that are not smaller in three weeks and healed in six weeks, should be considered malignant. The importance of adequate progress examination is stressed; if such progress studies are not possible, surgery is recommended. By observing all the diagnostic criteria outlined and obtaining frequent progress studies, the diagnostic error should be within the range of operative mortality.

Intensive and adequate medical therapy should result in prompt healing of the benign ulcer with no evidence of recurrence in at least 50 per cent of the patients followed for five years. An additional number of patients will make satisfactory progress, provided they continue their medical therapy.

The operative mortality for gastric resection is low and few recurrent ulcers develop following this operation for gastric ulcer. However, in approximately 10 per cent of the patients subjected to gastric resection other troublesome sequelae develop, such as persistent anemia, malnutrition, "dump" syndrome and diarrhea.

The majority of patients with gastric ulcer should receive adequate medical therapy rather than surgery because: 1) the incidence of malignant transformation of benign gastric ulcer is so low, 2) the diagnostic differentiation of benign and malignant ulcer is fairly accurate, 3) adequate medical therapy is satisfactory in a large percentage of the patients and 4) some patients have distressing side reactions from gastric resection. We deplore the growing tendency to regard every gastric ulcer as a surgical lesion, and routinely to advise operation on every such patient.

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CARCINOMA OF THE PROSTATE

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Carcinoma of the prostate is a common disease, accounting for between 15 and 20 thousand deaths each year in this country (1). Although rarely noted in men less than 40 years of age, the incidence rises steadily with increasing age thereafter (2). The number of elderly males in the general population will increase, since life expectancy generally is increasing, so there is every reason to believe that this cancer will become even more common. Studies of multiple sections of the prostates obtained from routine autopsies on males over 50 years of age have revealed histologic evidence of carcinoma in approximately 15 to 20 per cent (3, 4, 5). Although many of the cancers revealed by these detailed studies are extremely small and clinically not detectable, the evidence that the process had actually begun cannot be ignored. The relatively large difference between the histologic incidence and the clinical incidence of this growth provides some evidence that prostatic carcinoma can remain clinically inactive for many years, as if awaiting some unknown activating power to release its malignant potential. Approximately 20 per cent of the patients admitted to the New York Hospital for prostatic disease have had prostatic cancer. If the carcinoma has already developed to clinical proportions approximately 85 per cent of these patients will die within the next five years, if untreated (6, 7). Carcinoma of the prostate is, then, a common and serious disease which will become even more common clinically over the next several decades.

As in the case of most other neoplasms, the cause of prostatic carcinoma is unknown. Neoplasms have been induced in the prostates of animals, but under conditions which do not appear to approximate their natural occurrence in humans (8). The hormonal and metabolic changes of maturation and aging are certainly closely associated with the progress of this disease. Benign prostatic hypertrophy and prostatic carcinoma may be found separately or together in the same gland. It is generally thought that these two disorders are etiologically distinct. Benign prostatic hypertrophy begins in the central or in the periurethral parts of the prostate and as it increases, the true prostatic tissue is pushed and compressed laterally toward the periphery. Eighty-five per cent or more of the carcinomas begin in this peripheral or true prostatic tissue and only about 15 per cent originate within the more central hypertrophy (3, 4). Accordingly, the early clinical evidence of carcinoma is usually found by digital rectal examination. The usual prostatectomies for the correction of urinary obstruction remove only the hypertrophied tissue and leave the peripheral tissue. Accordingly, the fact that a patient has had a "prostatectomy" does

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not significantly safeguard him from carcinoma. A radical prostatectomy or subtotal perineal prostatectomy (9) does remove this peripheral tissue but these operations are not frequently carried out for noncancerous disease.

The overwhelming majority of prostatic cancers are adenocarcinomas. The neoplasm spreads beyond the prostate by three general routes, namely, by direct extension, by lymphatic spread and by venous metastases. The seminal vesicles are continuous with the prostate and lie in the same fascial space, so direct extension into them is common. The vesical outlet is likewise frequently invaded by direct continuity. Invasion of the rectum, however, is prevented to a significant degree by the protection afforded by Denonvillier's fascia. Rectal palpation will usually reveal extension into the seminal vesicles as firm, fixed induration. The normal seminal vesicles can barely be felt. Cystoscopic examination (particularly when combined with simultaneous rectal palpation), may demonstrate invasion of the vesical outlet, and biopsy transurethrally can establish this point. Histologically, perineural lymphatic involvement is frequently noted but it is interesting that there is no close relationship between the presence or absence of such involvement and the prognosis following radical perineal prostatectomy. Metastases to the pelvic lymph nodes are frequently found when the disease is locally advanced, having been found in all of 12 consecutive pelvic exenterations performed by us for this disease, as well as having been noted in autopsies. Batson has demonstrated venous connections between the area of the prostate and the lumbar spine and pelvis (10). Since nodal metastases are not invariably found in the presence of extensive metastases in the lumbar spine and pelvis, this mechanism described by Batson seems the most likely explanation for the frequent finding of metastases in these areas. Why patients with prostatic carcinoma often complain of lumbosacral backache and sciatica is easily understood. Secondary invasion may also occur via the systemic circulation, and deposits may appear in almost any organ. Metastases from prostatic carcinoma appear to have a predilection for bone but are by no means rare in the lungs, liver and lymph nodes.

The bony metastases are usually visible on x-ray films as blotchy, irregular areas of increased density and such a typical appearance in the lumbar spine and pelvis of a male past 50 is almost diagnostic (Fig. 1). Paget's disease of bone sometimes causes confusion but, in general, Paget's disease is more diffuse, and the increased trabecular markings and cortical thickening within the areas of Paget's disease are usually differentiated from the complete lack of pattern within the bony densities of metastatic prostatic cancer (Fig. 2). Not all prostatic metastases produce this typical picture and some of them produce the moth-eaten, melted away, osteolytic changes which are seen with many other types of carcinoma which may metastasize to bones (Fig. 3). If there is much osteoblastic activity, or if hepatic function is impaired, the alkaline phosphatase concentration of the serum increases. Accordingly, most patients with osteoblastic metastases from carcinoma of the prostate, as well as those with Paget's disease (also growing children, patients with healing fractures, patients with bone-producing neoplasms, and those with certain hepatic dis-

orders) have an increased concentration of alkaline phosphatase. Even though the alkaline phosphatase level is not a highly specific diagnostic aid, repeated determinations may provide some indication of the trend of osteoblastic activity. The acid phosphatase is a separate enzyme from the alkaline phosphatase

FIG. 1. Osteoblastic and osteolytic metastases in sacrum and pelvis, from carcinoma of prostate. Pathologic fracture in osteolytic area of right pubic bone.

and is a much more specific indicator of prostatic activity. Practically speaking, prostatic tissue is the only significant producer of acid phosphatase in the body, the enzyme being in fact a secondary sex characteristic of chemical nature (11, 12). From present data, it would seem that this enzyme is normally excreted into the urine, so that the level of the acid phosphatase in the blood remains fairly low. This normal situation appears to prevail when benign pros-

tatic hypertrophy is present and also when the prostatic cancer is still limited to the confines of the gland. On the other hand, extension beyond the original limits of the gland, especially by metastasis, permits more ready absorption into the serum, so that the serum acid phosphatase level rises. At any rate, an elevated acid phosphatase level nearly always indicates the presence not only of prostatic carcinoma but also of its extension beyond the confines of

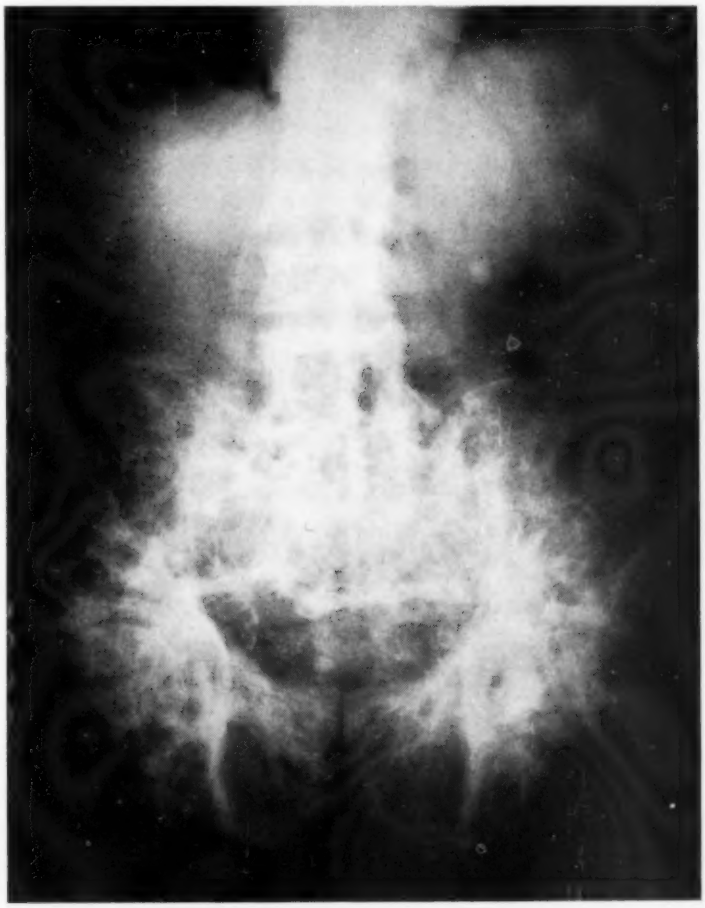

FIG. 2. Marked Paget's disease in sacrum and pelvis. Note trabeculations

that gland. The exceptions to this rule are rare and are usually found to be based on laboratory error. However, prostatic trauma, infarction, or massage can produce temporary rises in the level of serum acid phosphatase. We have recently encountered 2 cases of agnogenic myeloid metaplasia in which the concentration of serum acid phosphatase has been repeatedly found to be elevated, yet there is no evidence of major prostatic disorder in either instance (final studies of these cases have not yet been completed). Certainly the burden of proof rests heavily on the physician who considers that his patient's elevated serum acid phosphatase level is due to some disorder other than extensive prostatic carcinoma. In other words, the diagnostic value of an elevated serum

acid phosphatase level, when present, is very great; but the excluding value of this test, although significant, is by no means so reliable. About 20–25 per cent of prostatic cancers produce so little acid phosphatase that an elevation of the serum level does not occur, even in the presence of widespread bony or

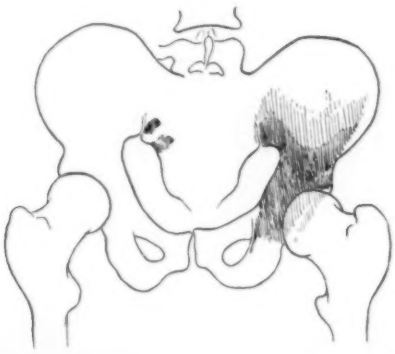

FIG. 3. Osteoblastic metastasis from prostatic carcinoma, particularly about left acetabulum.

soft-part metastases. It is obvious also that a certain critical small amount of extension or metastasis is necessary to produce an elevation, even when the carcinoma is a vigorous producer of acid phosphatase.

In the typical example of prostatic carcinoma with metastases to bone, the x-ray evidences of increased density in the usual metastatic area are coupled with an elevation of the serum phosphatases, both alkaline and acid. When

these circumstances are clearly demonstrated, a diagnosis of prostatic carcinoma with spread beyond the prostate is established. The reverse situation, although significant, does not reliably exclude the diagnosis.

Prostatic tissue produces several other enzymes, among which is fibrinolysin (13). Occasionally this fibrinolysin can be detected in the blood stream when the prostatic carcinoma from which it has originated has spread beyond the confines of the gland. The presence of this enzyme in the blood stream can be a cause of spontaneous bleeding (such as epistaxis, petechiae) or postoperative hemorrhage. In such patients the bleeding and clotting times may be normal. Fibrinolysin in the blood may be detected by tests for the dissolution of the blood clot by the enzyme (dissolution of the clot within a 24-hour period, when the specimen is incubated at 37°C., is the most readily available test). Surgeons should bear this possibility in mind regarding any patient with possible prostatic carcinoma, particularly if there is any suggestion of abnormal bleeding. Fibrinolysin in the blood stream appears to vary from time to time in the same patient and it may be reduced by the hormonal therapy to be described.

Clinical Diagnosis

In clinical practice there are three general classes of patients in whom the diagnosis of prostatic carcinoma is made. The first consists of those patients in whom an asymptomatic but suspected area limited to the prostate is found by an alert doctor in the course of examination. Usually these are the patients with the real hope for cure. Furthermore, this group could be increased at the expense of the next group to be mentioned, if physicians were generally alert to the frequency and the possibility of this common disease. The next class consists of those patients who come to the physician for symptoms due to metastases. Unfortunately, this is still the largest single group of patients. The male with sciatica beginning after the age of 50 without obvious cause, is always a suspect. If the sciatica is bilateral and if the patient is 60 or over, the diagnosis is more likely to be prostatic metastases than anything else. Interestingly, the pain from the metastases is often worse at night. Occasionally, a prominent distant metastasis produces the presenting symptoms, *e.g.*, in one femur, in the cervical spine, in one rib, or in a cervical lymph node. Naturally, systematic study of these cases usually provides many other diagnostic indications, but the most readily available single measure is the rectal palpation of the gland. The third class of patients seen in practice consists of those with complaints of prostatism, frequency, poor stream, nocturia, urgency, residual urine and, at times, hematuria. The patient in the prostatic carcinoma age group, who gives a relatively brief history of unremittingly progressive prostatism, is particularly suspected of having carcinoma. Naturally these three groups of patients overlap, especially with increasingly careful study. Thus, it is not rare to find a patient with prostatism and also with symptoms of metastases.

From the foregoing facts, the steps to be taken in making a clinical diagnosis should be easily appreciated. They are:

1. Palpation of the prostate by rectal examination. Variations in the con-

sistency of the prostate are suspect and if the areas are hard and irregular, the burden of proof is to demonstrate that they are not carcinoma. A recent active infection may produce results which are deceiving. However, the patient's history and urinalysis usually indicate infection; and, what is more

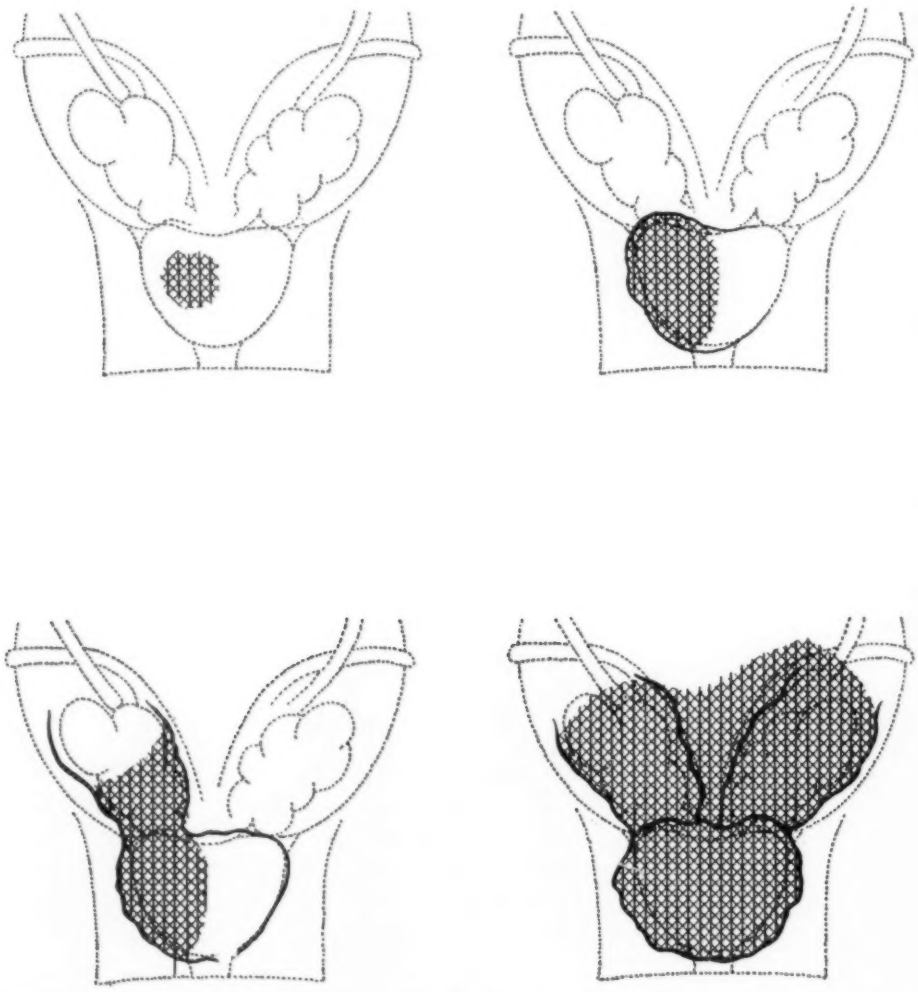

FIG. 4. Diagrams of typical findings on rectal palpation, as a carcinoma might advance. Dotted lines indicate normal configuration; solid lines, the changed outline; and the cross-hatching of three lines, stony consistency.

important, with simple therapy a change toward the normal occurs within one or two weeks. The most typical finding is a stony-hard area in the posterior surface of the prostate, area is fairly discrete and which, within itself, is nodular or granular. When the cancer has developed further, gross asymmetry of the prostate, further variation in consistency, partial fixation of the gland, induration, and a mass extending into the seminal vesicles can be noted (Fig. 4). A few prostatic cancers are soft and, as noted before, about 15 per cent begin

within hypertrophy, so that the diagnosis in early cases of these sorts may be difficult. Occasionally, a prostatic calculus causes some difficulty in differentiation. The fact remains, however, that the rectal palpation of the gland is the most practical single measure leading to the diagnosis of prostatic cancer.

2. When the suspicion of prostatic carcinoma has been raised, x-ray examination of the lumbar spine and pelvis and the determination of the serum alkaline and acid phosphatase levels are next in order. As discussed earlier, the diagnosis may be conclusively established at this point. In addition, a radiograph of the chest is needed, because metastases to the lungs and ribs are not rare.

3. The examination of the urine sediment after a prostatic massage, or the examination of the semen, by the Papanicolaou technique, will often provide objective evidence by demonstrating the presence of cancer cells. When such a demonstration has been made by an experienced pathologist it can be relied upon, but one must remember that other tumors may be present in the urinary tract, especially carcinoma of the bladder. The value of this cytologic technique in excluding the presence of a carcinoma of the prostate is, on the other hand, decidedly limited. The small potentially curable carcinoma located in the periphery of the gland usually exfoliates too few cells into the urine to permit its detection in this way. In spite of its limitations, the Papanicolaou technique has proved itself a valuable aid to the clinical diagnosis of prostatic cancer, especially in cases of difficult differentiation when the gland is more than minimally abnormal. The place of this technique in the screening of patients for the detection of early and unsuspected carcinoma of the prostate is now being studied, but the data available at present do not permit a reliable statement.

4. The most conclusive step in diagnosis is biopsy. This may be performed by needle aspiration or the use of one of the small punch instruments through the perineum. If the lesion is small, the operator is seldom sure of having tapped the proper area; therefore, a formal open biopsy via the perineal route is usually the method of choice. When the gland is massively involved with tumor, aspiration or punch biopsy is much simpler technically and usually provides adequate tissue for the diagnosis. Pathologic interpretation of the findings in material from aspiration biopsy specimens requires some experience. When the carcinoma has advanced, the transurethral excision of tissue will often provide adequate material; but if the lesion is early and in the periphery of the gland, the transurethral excision may not reach it. In the final analysis, perineal exposure and adequate removal of the suspicious area is the most conclusive single step to be made in order to demonstrate the presence of the disease and, in the face of continued suspicion, is the step required when all other methods have failed.

Treatment

The treatment of prostatic carcinoma may be discussed as curative, palliative or investigative:

Curative. The only cure for prostatic carcinoma is radical total excision of the gland, together with enough adjacent tissue to provide a margin of safety. Cures have occasionally been reported by other modalities, notably radiation

and hormonal therapy. However, the occasional spontaneous remissions could account for most of these rare reports. In addition, close scrutiny of the records in these cases often reveals that a definitely positive diagnosis (by biopsy particularly) was not established, or that the follow-up period was not long enough to be significant. Reliable cure rates for prostatic carcinoma are best based on a 10-year follow-up, but practical considerations justify the 5-year standard.

Radical perineal prostatectomy, as perfected by the late Hugh Young, has given a 5-year successful-result rate between 25 and 50 per cent (usually 30 to 40 per cent) (14). The really discouraging item is that the patients with neoplasm suitable for this procedure are in a decided minority, constituting from 5 to 10 per cent of all patients seen with prostatic carcinoma. In other words, 90 per cent of the patients with this disease have such progression by the time they reach the urologist that Young's operation is not applicable. Clinical studies are currently being made in an attempt to determine whether there is another group of patients upon whom pelvic exenteration with bilateral lymph node dissection might be carried out. There appears to be a group in which the carcinoma is too extensive locally for Young's operation, yet is not extensive enough to be beyond circumvention by pelvic and nodal exenteration (15). At the present moment 2 of 12 such patients operated upon more than two years ago are free of clinical evidence of cancer, but these results must be considered inconclusive. Incidentally, the number of 5-year successful results could be quite small, yet significant, considering the amount of progression already present in such cases. There are other limitations to Young's operation besides the fact that it does not cure all patients. Impotence is the rule after this operation, but considering the age of most candidates, particularly in view of their potentially fatal disease, this seems a small price to pay for a good prospect of cure. Rarely a fistula results, but most of these can be subsequently closed. Incontinence or some degree of poor urinary control is a common outward effect, but the incidence of this result varies according to the surgeon who performs the operation. Unfortunately, little can be done for the permanent correction of the incontinence, except the use of a penis clamp. Poor urinary control does not by any means result in all cases. At least 75 per cent have reasonably satisfactory control within three to six months after operation. It is important to remember that patients do not die of urinary leakage by itself, but they do die of cancer by itself. Whether castration should be carried out at the same time as Young's operation, is not generally agreed upon. The testes postoperatively are of little value, except cosmetically; moreover, there is some reason to suspect that patients not actually cured by the operation may receive worthwhile benefit of the sort to be discussed.

Palliative. The palliative program has much to offer to that vast majority of patients with disease not amenable to cure by any known method. Lives are definitely prolonged and, most particularly, much suffering is relieved (6). The relief of urinary obstruction is usually best accomplished by transurethral resection, as it is the least disturbing to the patient, may be repeated if necessary, and gives a prompt effect. Minor degrees of obstruction often subside during

the hormonal therapy to be described; but usually major degrees of obstruction do not respond in sufficient degree, or promptly enough, to hormonal therapy alone.

The epoch-making discovery that the sex hormones can and do influence the course of this disease in approximately 90 per cent of the cases is the most important single consideration in the palliative treatment of patients with carcinoma of the prostate. Munger noted a marked clinical improvement in a high percentage of his patients with prostatic cancer who had had radiation therapy to the testes (16). Although occasional efforts in this direction have been made over the past sixty years, with equivocal or negative results, it remained for Huggins and his associates to coordinate both old and new knowledge from the laboratory and clinical practice in the form of an understandable and workable program of palliation by hormonal therapy (17–19).

The rationale of endocrine therapy in the human is based largely upon the experimental observations in the dog, particularly those made by Huggins and his associates. Androgen promotes prostatic activity, including the activity of most prostatic cancers; the removal of androgen by castration usually produces a beneficial effect. This effect on the patient with advanced prostatic cancer is usually prompt (often appearing within a few hours) and is frequently dramatic. As will be noted later, castration does not remove all of the body's androgen. The obviously suggested trial of substituting estrogenic hormones for castration has been made, and some authorities prefer estrogenic therapy to bilateral orchiectomy. The expense of estrogenic therapy is rarely sufficient to be a disadvantage. If the patient is liable not to take medicines regularly, estrogenic administration is obviously not as good as castration. Engorgement and tenderness of the breasts during estrogenic therapy is the rule but this condition is not serious and almost never requires additional measures, except reassurance. The effect of estrogenic therapy is slower to appear than the effect of castration, so that for the severely ill patient who needs prompt relief, castration seems preferable. Diethylstilbestrol is the most commonly used estrogen but others are also effective. One milligram of stilbestrol twice a day indefinitely, is a common maintenance dosage. There is no clear evidence that any one estrogen is superior to others. Huge doses have been tried and on occasion some additional improvement, at least subjectively, has been obtained. Progesterone, 100 mg. by injection daily, is usually capable of producing essentially the same results as the administration of oral estrogen, but the progesterone is relatively expensive and it is not administered with the same ease (20).

Whether estrogenic therapy or castration is the more effective, or whether they should be used in combination, or whether hormone therapy should be instituted as soon as the diagnosis is made, regardless of symptomatology, are matters upon which there is not yet general agreement. It appears that castration alone is somewhat more effective than estrogenic therapy alone, and there are some statistical suggestions that simultaneous combined therapy is more effective than either program singly (6). Occasionally special circumstances indicate the form of therapy: for example, the patient with cardiac failure may

retain too much fluid during estrogenic therapy and therefore be better controlled by castration. It seems evident that the patient with symptoms should receive hormonal therapy promptly, but it is still an undecided question whether the asymptomatic patient should or should not be merely followed until symptoms appear. It is our inclination to institute both forms of therapy simultaneously at the time the diagnosis is established in those patients not suitable for radical excisional therapy.

The remission obtained by hormonal therapy occasionally lasts for many years, and remissions lasting two to three years are not unusual. The average remission, however, is approximately eleven months, and a small percentage of patients obtain no significant remission by hormonal therapy. When only one form of hormonal therapy has been used originally, a second remission can occasionally be obtained by the use of the other modality. Such secondary relief can rarely be obtained by increasing the dose of estrogen or by the use of progesterone. These secondary remissions are usually incomplete and of much shorter duration than the primary benefit; so the possibility of their occurrence is not actually a significant argument against the use of combined castration and estrogenic therapy from the beginning.

The remission produced by treatment with hormones can usually be observed not only symptomatically but also objectively by noting the fall of the serum acid phosphatase level. If the serum alkaline phosphatase level is elevated, it usually returns toward normal slowly and, in fact, there is frequently a brief increase immediately after therapy has been instituted. Regression, as noted radiographically, is variable and indeed not always of the same degree in different locations. Although complete disappearance of the radiographic evidence is known, such an occurrence in advanced cases has been exceedingly rare (Figs. 5 and 6). A regression toward normal in the bulk and consistency of the involved gland is usually well marked, as noted on rectal palpation.

The end of a remission is sometimes heralded by a rising serum acid phosphatase and/or alkaline phosphatase level, but the interpretation of such findings at this stage is subject to many variations. Reappearance or progression of lesions may be noted radiographically and further progress may be detected by rectal examination. Most impressive, however, is the fact that the patient's symptoms reappear.

Neurosurgical procedures such as bilateral thoracic cordotomy, root section and intrathecal injection of alcohol for the relief of pain still have a place in the palliative management of this disorder, although this place has become less prominent because hormonal management gives such excellent symptomatic relief and appears to slow the fatal process. Furthermore, after the cancer has become refractory to hormonal control, life expectancy is often too brief to warrant extensive purely palliative measures. The cautious injection of alcohol intrathecally is carried out with relative ease and sometimes produces enough relief of pain to warrant a trial, even at the risk of disturbed vesical function or other neurologic sequelae. Radiation therapy to the painful areas is frequently valuable for the relief of pain, even though such relief may not be permanent.

Investigative. The investigative programs for the control of prostatic cancer are of great academic interest and hold promise for future clinical application. These programs are numerous and varied and cannot all be considered here.

As just mentioned, the regression in the tumor as felt on rectal examination is often marked. This has suggested that hormonal therapy might reduce the locally advanced neoplasm to such an extent that Young's radical operation would become feasible. Optimistically this might happen; but the greater

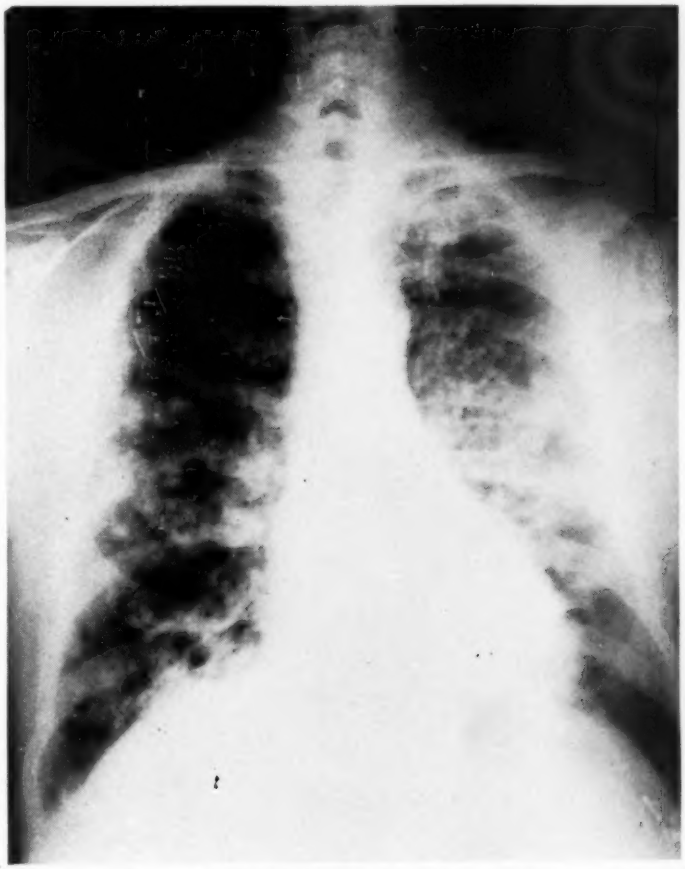

FIG. 5. Roentgenogram of chest showing extensive metastases from prostatic carcinoma.

likelihood is that, even though the carcinoma were to become somewhat smaller and softer, it would not draw in its octopus-like extensions.

Perhaps the most important among the investigative-palliative forms of therapy is bilateral adrenalectomy (21). In theory, this procedure removes certain hormones which promote the activity of the cancer. The operation itself is not difficult, but substitution therapy is imperative in order to prevent a fatal result. Only since the availability of cortisone, has bilateral adrenalectomy been feasible. The management of these patients has now been fairly well established, so that death from adrenal insufficiency has become uncommon.

Some reports indicate dramatic remission and most reports indicate that there has been some improvement, usually of a subjective nature. Our experience with 12 bilateral adrenalectomies in cases of advanced carcinoma has been disappointing from a practical point of view (22). Most of our patients obtained a moderate degree of subjective improvement (particularly in the reduction of pain), but really dramatic relief and rehabilitation to an active life has been an exception. Furthermore, in our experience, the remissions produced by bilateral

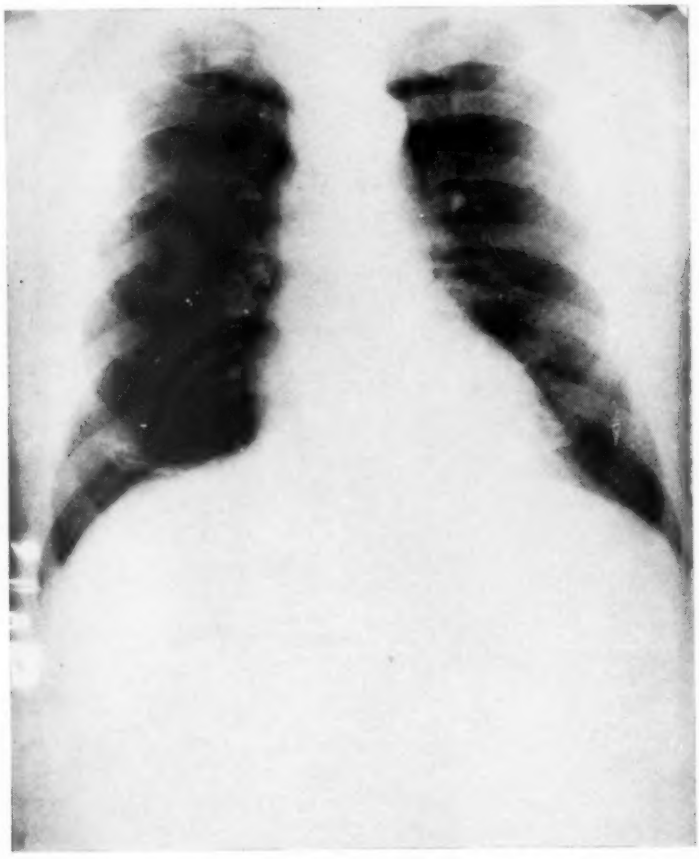

FIG. 6. Roentgenogram of chest of same patient, twenty months after castration and estrogen therapy. The regression of the neoplasm is unusually marked.

adrenalectomy have been usually incomplete and brief. Unfortunately, there is no currently available means of predicting which patients will receive worthwhile alleviation from this form of therapy.

The removal of the pituitary gland has been considered and has actually been attempted in a few instances. This procedure is so new and has been performed upon such a small number of patients that no real evaluation can be made at this time. The administration of cortisone and of nearly every available hormone has been tried, but no clearly advantageous program has yet been demonstrated from this direction. New methods of radiation therapy are constantly being

evolved; one of the more promising now being investigated is the use of radioactive colloidal gold by direct injection into the prostate (23). The possibility of cures by new excisional techniques has been mentioned earlier. For obvious reasons these experimental modes of therapy are not for the surgeon who operates only occasionally, and should be confined to well-equipped and well-staffed institutions, until their position is accurately delineated. On the other hand, they do offer something to the patient whose tumor has become refractory to the more standardized modes of therapy.

SUMMARY

Cancer of the prostate is a common disease. Rectal examination of the gland is the most practical single diagnostic measure. With few exceptions, elevation of the serum acid phosphatase level indicates not only the presence of carcinoma of the prostate but also spread of the neoplasm beyond the confines of the gland. Osteoblastic metastases noted in the lumbar spine and pelvis by radiography are highly suspicious and, when combined with elevated levels of acid and alkaline phosphatase, are diagnostic. The male past 50 in whom lumbosacral backache and sciatica develop without evident cause, is very liable to have prostatic cancer with metastases. Biopsy is the final conclusive step to prove the presence of this cancer. Young's radical perineal prostatectomy produces five-year successful results in a reasonably high percentage of patients whose condition permits this operation. Unfortunately, most patients show such progress of the disease that this valuable operation is usually not applicable. Palliative therapy prolongs the life and relieves the suffering of the majority of patients with advanced prostatic carcinoma. Chief among the measures used in the palliative treatment is the hormonal variation produced by castration or the administration of estrogens, or both. New methods of therapy are being actively investigated and they hold promise for the future.

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INTESTINAL OBSTRUCTION IN THE AGED*

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Intestinal obstruction is a hazardous surgical problem. It is even more dangerous in the aged individual. The physiologic upset incident to the obstruction calls for an extraordinary response, and in the aged the body mechanisms are relatively inelastic and lack the reserve found in a younger person. If the obstruction is in the small bowel, aside from the local changes in the bowel itself, the outpouring of serum and loss of electrolytes from vomiting may not be rectifiable if present for a prolonged period, because of irreversible changes resulting indirectly from the patient's age and poor reserve. In addition, a type of obstruction frequently occurs in the aged which is rarely seen in the young. This occurs in the large bowel with the creation of a "closed loop" obstruction. The superimposition of distention of the colon on an already impaired blood supply to the gut creates a situation in which great danger of perforation with resultant peritonitis exists. Such a perforation may develop with surprising rapidity and frequently leads to death. This study has been made to point out some of the pitfalls in the management of the aged patient with intestinal obstruction and to suggest how such accidents may be avoided.

This review covers cases of proved intestinal obstruction during the years 1945–1951 inclusive at the University of Iowa Hospitals. Only individuals 65 years of age or over are included in this analysis. In this group there were 92 patients, and of these, 55 were males and 37 were females. There were 23 deaths in this series with an over-all mortality rate of 25 per cent. Table 1 lists the incidence of obstruction by years with the accompanying mortality rate. The mortality rate in 1945 was 44.4; in 1946, 25.0; in 1947, 29.4; in 1948, 33.3; in 1949, 23.0; in 1950, 28.0; and in 1951, 9.0 per cent. Table 2 lists the causes of obstruction. It will be noted that the greatest incidence was in carcinoma of the left side of the colon. However, surprisingly, a large number of cases were due to small bowel obstruction.

Ten patients had perforations of the bowel; and of this group, 5 died. (These are catalogued in Tables 3 and 4.) Of the 5 deaths, 4 occurred in the years 1945–1947, and 1 in the year 1949. One moribund patient died shortly after admission, and there was no opportunity to treat him. The other 4 patients were treated conservatively with long tubes connected to Wangensteen suction apparatus, and death possibly could have been prevented by immediate surgery without an attempt at tubal deflation; if these 4 deaths had been prevented, the mortality rate in this series would have been 20.6 per cent. These 4 cases presented similar problems. One patient had a volvulus of the right colon, and

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he was treated for forty-eight hours without success by means of suction, utilizing a Miller-Abbott tube. When it was noted that he had become more severely ill he was operated upon, and a perforation of the cecum with a generalized peritonitis was found. A hemicolectomy and ileocolostomy were performed, but he died shortly afterward. Another patient had a carcinoma of

TABLE 1

Mortality by Years

	1945	1946	1947	1948	1949	1950	1951	Totals
Number of cases	9	8	17	9	13	14	22	92
Deaths	4	2	5	3	3	4	2	23
Mortality per cent	44.4	25.0	29.4	33.3	23.0	28.0	9.0	25.0

TABLE 2

Causes of Obstruction

Cause	*No. of cases*
Carcinoma of sigmoid colon	16
Adhesive bands	14
Carcinoma of rectosigmoid	9
Strangulated hernia	9
Carcinoma of rectum	7
Carcinoma of splenic flexure of colon	6
Volvulus of small bowel	5
Diverticulitis of colon	3
Carcinoma of hepatic flexure of colon	3
Carcinoma of ascending colon	2
Carcinoma of transverse colon	2
Volvulus of sigmoid	2
Carcinomatosis	2
Obstruction; diverticuli of small and large bowel	2
Carcinoma of descending colon	1
Carcinoma of cecum	1
Carcinoma of cervix, with invasion	1
Volvulus of right colon	1
Lymphoma of cecum	1
Carcinoma of pancreas, invading colon	1
Carcinoma of uterus, invading colon	1
Inflammatory obstruction of rectosigmoid	1
Gallstone obstruction of ileum	1
Intussusception of colon into rectum	1
Total	*92*

the sigmoid. He was treated with suction through a Miller-Abbott tube, and he received repeated enemas. After two days he suddenly lapsed into severe shock and expired a short time later. The cause of death was perforation proximal to the malignancy, and generalized peritonitis. The third patient was treated for six days by means of suction, using a Miller-Abbott tube. His distention continued to increase. He complained on the seventh day of sudden pain in the

abdomen, passed into a severe shock-like state, and died shortly afterwards. This picture is not infrequently seen with a perforation and overwhelming peritonitis. The fourth patient had a carcinoma of the splenic flexure. After twenty-four hours of attempted decompression with suction, utilizing a Cantor tube, it was recognized that a perforation had occurred at the cecum, and a cecostomy was performed. He received both penicillin and streptomycin but expired soon after the operation.

Of the 5 patients with perforation who lived, 1 had carcinoma of the splenic flexure with a perforation proximal to the carcinoma. He had an immediate

TABLE 3

Perforations of Bowel

Description	*Result*
1. Carcinoma of rectosigmoid with performation of diverticulum and peritonitis—1945. Death occurred, without treatment, shortly after admission.	Died
2. Volvulus right colon with perforation of cecum—1945. Treated with Miller-Abbot tube for 48 hours; then right hemicolectomy and ileocolostomy.	Died
3. Carcinoma of splenic flexure with perforation—1947. Had cecostomy followed later by resection; surgery not delayed; received penicillin.	Lived
4. Carcinoma of sigmoid with perforation—1947. Treated with Miller-Abbott tube and repeated enemas.	Died
5. Carcinoma of sigmoid with perforation—1947. Treated with Miller-Abbott tube for six days without relief.	Died
6. Diverticulitis of colon with perforation—1948. Treated by transverse colostomy and penicillin.	Lived
7. Carcinoma of splenic flexure with perforation of cecum—1949. Treated with Cantor tube for 24 hours; then operated upon with closure of perforation and cecostomy; received streptomycin and penicillin.	Died
8. Volvulus of small bowel about a fibrous band with perforation of ileum—1949. Treated by immediate operation with resection of ileum and anastomosis; received penicillin and streptomycin.	Lived
9. Carcinoma of transverse colon with perforation of cecum—1950. Treated by immediate operation with resection of ascending colon and anastomosis; rereceived penicillin and streptomycin; later drainage of subhepatic abscess.	Lived
10. Small bowel obstruction from adhesive band, with perforation of ileum—1950. Treated by immediate resection of ileum and cecum and anastomosis; received penicillin and streptomycin; acute cholecystitis, which developed nine days postoperatively, was treated by cholecystostomy.	Lived

cecostomy and received large doses of penicillin. He finally recovered sufficiently to have a bowel resection. This is unusual; a perforation from an overdistended large bowel, as pointed out before, is usually fatal. Another patient had diverticulitis. A transverse colostomy was performed, and penicillin was given for several days. In this type of case, recovery usually takes place, because the slowly developing inflammatory process walls off the site of perforation and the infection is overcome spontaneously. A third patient had a volvulus of the small bowel about a fibrous band, and a perforation of the ileum. He was operated upon shortly after admission and had a resection of the ileum and an anastomosis. He received both penicillin and streptomycin and recovered. His perforation was of short duration and may account for the successful result

TABLE 4
Mortalities

Case No.	Year	Age (yrs.)	Diagnosis	Treatment	Cause of death
1	1945	81	Carcinoma of rectosigmoid	Colostomy	Uremia; diabetes*
2	1945	69	Volvulus of right colon	M-A tube, followed by hemicolectomy & ileocolostomy	Perforation of cecum*; peritonitis; atelectasis
3	1945	73	Carcinoma of rectosigmoid; diverticulitis of colon	None; died shortly after admission	Perforation of diverticulum*; peritonitis
4	1945	65	Diverticulitis of sigmoid, with stenosis	Colostomy, followed by resection and end-to-end anastomosis	Pulmonary embolus?
5	1946	76	Carcinoma of colon, with metastases	Colostomy	Metastases*; intraperitoneal abscess
6	1946	80	Obstruction at rectosigmoid	None	Pulmonary embolus?
7	1947	91	Carcinoma of sigmoid	M-A tube; repeated enemas	Perforation*; peritonitis
8	1947	74	Carcinoma of sigmoid	M-A tube	Perforation? Peritonitis
9	1947	71	Carcinoma of rectum	Colostomy	Pulmonary infarcts*; pneumonia; pleural effusion
10	1947	74	Carcinoma of pancreas, involving bowel	Ileocolostomy	Extensive carcinoma*; pneumonia
11	1947	71	Carcinoma of colon, with carcinomatosis	Ileocolostomy	Extensive carcinoma*
12	1948	76	Carcinoma of cervix, with invasion of rectosigmoid	Colostomy	Extensive carcinoma*
13	1948	68	Strangulated hernia	Died shortly after admission	Peritonitis?
14	1948	65	Adhesions and volvulus	Resection of ileum and ascending colon; ileocolostomy	Leakage of anastomosis*; peritonitis; pneumonia
15	1949	65	Carcinoma of splenic flexure	Cantor tube, followed by closure of perforation and cecostomy	Perforation of cecum*; peritonitis; atelectasis
16	1949	72	Carcinoma of rectum, with metastases	Colostomy	Pulmonary metastases*; pulmonary embolus

* Autopsy

TABLE 4—*Continued*

Case No.	Year	Age (yrs.)	Diagnosis	Treatment	Cause of death
17	1949	77	Volvulus of small bowel around jejunostomy	Reduction of volvulus; closure jejunostomy; gastrostomy	Carcinoma of esophagus? Pneumonia?
18	1950	69	Adhesions	Resection of ileum and ileocolostomy	Pulmonary edema*; azotemia
19	1950	66	Strangulated hernia	Resection of colon	Peritonitis*; central liver necrosis; pyelonephritis
20	1950	73	Volvulus of small bowel	Freeing of adhesions, and ileocolostomy	Volvulus of transverse colon*; wound infection; liver metastases from carcinoma of colon
21	1950	75	Intestinal obstruction following drainage of pelvic abscess after prostatic resection	None	Small bowel obstruction*; perivesical abscess; acute pulmonary edema; uremia; carcinoma of prostate
22	1951	79	Carcinoma of sigmoid	Operation started	Cardiac arrest*; luetic aortitis; carcinoma of sigmoid
23	1951	81	Adhesions in ventral hernia	Release of adhesions and repair of hernia	Coronary occlusion*; edema wall of ileum; right hydronephrosis, severe

in this instance. This case also points out the value of the antibiotics. A fourth patient had a carcinoma of the transverse colon with perforation of the cecum, and was treated by immediate operation with resection of the ascending colon and anastomosis. He received penicillin and streptomycin. A subhepatic abscess developed, which was subsequently drained. The fifth patient had a perforation of the ileum due to obstruction from an adhesive band. He also was treated by immediate resection and anastomosis, receiving both penicillin and streptomycin. An acute cholecystitis developed nine days postoperatively, and a cholecystostomy was performed.

DISCUSSION

It has been repeatedly pointed out that attempts to decompress the large bowel by means of a tube almost invariably end in failure and carry the added risk of possible perforation while this measure is being employed. There is also no point in temporizing by administering repeated enemas, for a bowel that is blocked by a neoplasm or inflammatory mass, with the consequent inevitable edema, will never be deflated in this fashion. Only surgical decompression is successful and should be carried out as soon as possible. It is equally hazardous to attempt a resection of the large bowel in the face of obstruction, as the usual

end-result is death from leakage and peritonitis, or the patient may be so depleted of necessary body metabolites that he cannot withstand an extensive surgical procedure.

The fact that 5 of these patients lived after perforation can be attributed in large measure to the antibiotics, the availability of blood, and the early surgery. We consider ourselves very fortunate that death did not occur in these instances, and these patients serve to re-emphasize that delay in operating upon these patients is fraught with great hazard.

All patients in the aged group who have intestinal obstruction must be considered as extreme emergencies. This has been pointed out before, most recently by Cutler (1). Approximately 50 per cent of the patients in this series had the site of obstruction in the large bowel. Usually this is due to malignancy. The complete obstruction of the lumen is not caused by the neoplasm itself, but by the associated infection and edema of the bowel wall. In this group the symptoms ordinarily are very mild, except for an occasional or intermittent gas pain or vague abdominal distress. The patient enters the hospital only when the distention and obstipation have become severe, in other words, when the obstruction has become complete and acute. Usually by this time the patient has experienced a marked weight loss. In other instances the visible abdominal distention may be mild, if at all recognizable. This is especially true of lesions in the right side of the colon, where, if the lesion is close to the cecum the distention may be sufficient to produce perforation of the bowel but may not be recognizable on examination of the abdomen. Not infrequently, these patients have not experienced any vomiting; and, if vomiting has occurred, it has consisted only of gastric or duodenal contents and is usually not severe.

Unless the physician is alert to this problem, the danger may be overlooked. A roentgenogram of the abdomen, with the patient either upright or in the supine position, will usually disclose the distended segment of colon. Rarely, an incompetence of the ileocecal valve is present, and some gas may also be detected in the ileum. A barium enema given as an emergency diagnostic measure will locate the site of the obstruction in the large bowel.

Immediate decompression by surgical means must be carried out, but only after rapid preliminary hydration and restoration of blood volume (2). Most of these patients are dehydrated, and thus hemoconcentration is present; consequently, when a blood examination is carried out, the high level of the hemoglobin value and red blood cell count may prove very deceptive. After proper hydration the hemoglobin level is frequently shown to be low; therefore, we feel that the best method of preparing these patients for an emergency operation is by means of blood transfusions. A Levin tube is passed and connected to a suction apparatus. If the lesion is in the rectum, a sigmoid colostomy is acceptable. If it is in the left side of the colon, a transverse colostomy is most satisfactory. For lesions in the right side of the colon an ileocolostomy is preferable to a cecostomy. A cecostomy may not only be dangerous to perform because of the marked distention and the thinness of the wall of the cecum, but it may also prove difficult to manage after it has been carried out. We have never been impressed

with the advantage of threading a tube by means of an enterostomy through the cecum past the obstruction. Surprisingly, an ileotransverse colostomy for a lesion in the right side of the colon not only relieves the obstruction but in a short while results in a decompressed segment of ascending colon. If the lesion is close to the cecum, the ileum is not distended, and the possibility of perforation of the cecum is very great, successful resection of the involved area with primary anastomosis may be carried out. As a general rule, however, decompression is much more satisfactory and safer. Some may prefer to perform a cecostomy for such a lesion. If so, the cecal surface should be placed so that an ample portion projects beyond the skin surface in order to prevent peritoneal contamination at the time the bowel is opened; usually this is rather difficult with a distended cecum.

After performance of a colostomy, if the distention is great, the margins of the bowel can be protected with vaseline gauze and a needle or a tube inserted, thus removing the gas. The fibrinous conglutination of the colon and tissue margins is so rapid that at the end of twelve hours the intestine can be safely opened without danger of peritoneal contamination. Later when the bowel has receded to normal size and is no longer edematous it is cleansed, and a resection and anastomosis can be performed.

In obstruction of the small bowel, the obstructive symptoms (such as cramp-like pain and vomiting) are usually abrupt in their onset and rapidly increase in severity. Borborygmi on auscultation, occurring synchronously with the abdominal cramp-like pain are very diagnostic, and the upright roentgenogram displaying distended small bowel loops confirms the diagnosis. Again, time must be taken to administer blood in order to rehydrate the patient and, at least partially, restore the blood volume. In addition, it is usually necessary to administer electrolytes in the case of the patient with obstruction of the small bowel, in contrast to the patient with obstruction of the large bowel. A Levin tube is passed and connected to the Wangensteen suction apparatus. In the aged individual a long tube should rarely, if ever, be used to decompress an organic small bowel obstruction; the procedure is of questionable value and postponement of surgery for a trial of this means of decompression, is dangerous. The risk of perforation and the difficulties associated with maintenance of fluids and electrolytes by parenteral means in the aged make immediate surgery mandatory as soon as the patient is in satisfactory condition.

At the time of surgery the simplest surgical procedure necessary to overcome the obstruction is performed. Resection is only carried out when definite gangrene is present. Cutaneous ileostomy should not be performed, as the loss of fluids and electrolytes from the bowel will usually be so great that shock will be rapidly precipitated, from acute dehydration and severe electrolyte loss. In such instances, when an ileostomy is considered, a short-circuiting procedure is a far more satisfactory operation. At the first signs of resumed peristalsis, the Levin tube is removed from the stomach. Close attention to blood levels of both sodium and potassium is essential; these levels can be maintained safely and satisfactorily only by reinstituting the normal intestinal flow. In the aged, attempts

to maintain normal electrolyte levels by parenteral means over many days is fraught with extreme danger.

The mortality in aged patients with obstruction will always be consistently higher than in younger patients. However, an effort must be made to keep this rate as low as possible. In this group, it can be done only by unhesitating surgery, after proper restoration of blood volume and electrolytes. Conservative management is not only dangerous but usually futile.

SUMMARY

1. Intestinal obstruction in the aged is very dangerous. Over a seven-year period the mortality rate has been 25 per cent.

2. A definite reduction in the mortality can be obtained by early surgery. Conservative handling of intestinal obstruction in the aged is extremely hazardous.

3. A method of management has been suggested.

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VARIABLE CONSTANTS*

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Mr. President, Members and Guests of the Geriatrics Society:

It is a great privilege to be with you tonight, to enjoy this bountiful repast and to prosper by the fellowship of the professional men and women who make up the roster of this society. After the felicitous remarks of your popular presiding officer, Dr. Thompson, I am reminded of the young physician who, unwilling to confine his efforts to the practice of medicine and feeling complete confidence in his extramural ability, made application as a speaker at one of our well-known agencies. The director of the agency was quite impressed with the material in the application and remarked to the young medico, "Well, you're quite a boy, aren't you? But are you such a good speaker?" "Yes," replied our doctor, "but there is just one thing the matter with me. I'm a little bit deaf." "What is that due to, young fellow?" asked the director. "Oh," said the medico "to the applause that always follows my speeches."

I can qualify as your speaker tonight on two counts. 1) I am no longer adolescent in chronologic sequence and am rapidly coming into the somewhat shadowy zone of geriatric placidity, although I hope that I am still a bit removed from second childhood, and 2) because the patients in my institutional practice in the last few years have become of such advanced age that I am shocked when I must examine one who does not have a crutch, retains all of his teeth and still has urinary control.

In the primitive tribes there were two views on the management of the aged, the sick and the crippled, according to Sigerist. One view was to succor the individual, make him happy, care for him and give him a place a bit above the mill-run of the tribe. The other was to do away with the poor soul. In the most primitive food-gathering, fishing and hunting communities there was better treatment of the aged and sick than in the more highly organized and less sharing organizations, where a tap on the head might solve the problem. In our own modern society we are taking care of our crippled and old but apparently with less and less of the personal, and more and more of the institutional relationship. "Put 'em in a home" seems to be the motto.

Every speech must have a title. It should be a pleasure to listen to a speech without a title. In this great city a few years back we had a famous surgeon who was not given a first name at his birth and so was called "Blank." This absence of a title did not seem to interfere in any way with the fine surgical skill with which he approached each operation. The title of this little contribution to the

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evening's message is "Variable Constants." What it means I do not exactly know, nor does my wife, nor my secretary, and I doubt if you will when I finish. So into the hopper goes the title and what comes forth may, in spite of everything, contain a few ideas of service.

As I have pointed out, the purpose of any medical meeting is to increase knowledge. This knowledge may be medical, ancillary, or concerning people and ideas. The purpose of the medical meeting is summed up in the translation of Paul Shorey's motto for the University of Chicago. Shorey was the Professor of Greek, but he came up with the Latin motto, "Crescat Scientia—Vita Excolatur." It was probably motivated by that portion of Tennyson's "In Memoriam" which reads something like this:

> Strong Son of God, immortal Love,
> Whom we, that have not seen thy face,
> By faith, and faith alone, embrace,
> Believing where we cannot prove;
>
> We have but faith: we cannot know;
> For knowledge is of things we see;
> And yet we trust it comes from thee,
> A beam in darkness: let it grow.
>
> Let knowledge grow from more to more,
> But more of reverence in us dwell;
> That mind and soul, according well,
> May make one music as before,
> But vaster.

Charles Henderson, the learned Chaplain of the University in the days when students were required to go to chapel, even though they were medical students, gave it a designing translation when he said "Let knowledge grow from more to more—and life be enriched." Our objective then becomes to enrich our lives in many, many directions as our knowledge grows from more to more.

Did you know that the term "geriatrics" is not included in one of our better encyclopedias? You should protest loudly, for old age is discussable at any and all times and should bear the more modern name of "geriatrics." "Gerontic" is such a depressing word, for it refers to an old man—the women are left out. The word "gerontine" denotes a crystalline base with a formula $C_5H_4N_2$ and is derived from the liver and kidneys of old dogs. The base gerontine is an isomer of cadaverine. Nothing could be more significant than that we should put all of the old dogs up in brine. So we might suggest that the society change its name to "The Salty Old Dogs Pickled in Brine." But if the encyclopedia did forget you, the Bible did not, for you surely remember the directive to Titus from Paul—"that the aged man be sober, grave, temperate, sound in faith, in charity and in patience." But the wise old Paul also said that the aged woman should not be given to too much wine and a teacher of good things. So, you salty old

dogs, be sober and temperate here in this city of Chicago where so many things bad are just talk, and all are far outweighed by fine culture, beautiful music and unexcelled professional schools. In unstudied relaxation, enlarge the horizon and enrich life.

For those of you who are interested in old age and the Bible, I would direct your attention to the paper of Louis Krause on a Biblical Introduction to Geriatric Medicine given about a year ago before the Annual Meeting of the American College of Physicians and published later under the title of "Old Age in the Bible and Poetry" in the January 1952 issue of the Annals of Internal Medicine. In a different light was the skit given at one of our local clubs not long after Krause read his paper. A lone male cast on a desert island, looking about, saw no living soul, no sound did he hear. In anguish here he was, all alone, the last living human soul. And with that, he fell dead. And just at that moment from behind a tree stepped a huge male ape and a female ape; looking down in anguish they cried, "Now do we have to start that same thing all over again!"

Most of us here tonight were brought up to believe that a constant was a constant. We heard of the constant of gravitation, of the constant of capillarity, of the constant of integration, of the dielectric constant of quartz, or of that numerical quantity expressing a fixed relation, or of the natural property which retained the same value throughout an investigation; also there was the allusion to the constant of the sea where a steady wind cannot be expected, especially in the part between the trade-wind belts, sometimes called the doldrums. Ah, there we have it! We are down in the doldrums when we are short of wind, when there is no more about, no tank of oxygen, no fan, no motor, just out of wind. We become full of ennui and tedium from listening to this souped up prolixity by your essayist now in the doldrums with no hope of even a breeze to blow him out. But hope is not all gone! Some time ago I listened to a fine speech, but I must confess that I did not understand too much of it. However, one idea was worth the price of admission. It seems that since Einstein enlightened us on relativity, nothing is a constant. With the coming of the atomic age the only constant is the certainty of the uncertain, and the uncertainty of the certain. The one constant, then, is that the certain is uncertain. But let us take a little look at our own business. You all appreciate that I represent merely a practicing physician who must meet the same problems as you do in daily practice and in daily living, and must look back upon the successes and the failures of the years now spent, just as you do; but who also feels that the work of the present is much more important.

I am activated by the philosophy of the great physician of Baltimore who traveled down from our good neighbor to the North, on to Philadelphia and to Baltimore and thence across the sea to Oxford, and who said on the occasion of his farewell dinner, "I have but three personal ideals—one, to do the day's work well and not to bother about tomorrow. The second ideal has been to act the Golden Rule, as far as in me lay, toward my professional brethren and toward the patients committed to my care. The third has been to cultivate

such a measure of equanimity as would enable me to bear success with humility, the affection of my friends without pride, and to be ready when the day of sorrow and grief comes, to meet it with the courage befitting a man."

Summed up, it is the philosophy of living for the day—in which the task will be done as well as possible. It is the acceptance of the past and belief in the future, with interest deep in the present. For most of us, this is a full objective. How easily future plans may be upset by the soothsayers and seers of today, and with what startling rapidity can we be ruined by the stroke of the pen of a confused personality! We are appalled at the ease with which the impotent experiments of Europe have been seized upon and implemented into our daily activities. But I believe that the uncertainty of the certain is balanced by unchanging constants, often left deserted by the wayside—devotion to the task in hand, honesty in our approach to problems, courage in action, righteous forbearance, appreciation of the gifts of fellow practitioners and tolerance to the sincerity of friend or foe.

Whether we live and work by the lessons of the Old Testament or by those of the New Testament, whether we be immersed or baptized by water from above, whether we be black, white or yellow, whether we look to the sun or to the moon or prostrate ourselves before Allah, you and I as practitioners of medicine by the bedside, and inside or outside of hospitals, have a wonderful job to perform; for to treat the sick and to accept the responsibility of the intimacy of professional work is a job. "Come into the hospital and we will see you through," said Lipscomb. The practice of medicine knows only the boundary of courageous honesty. Man's ills cannot be documented or compartmented or sealed in pigeon holes. To heal the sick is a job, a job rarely given to one man alone but to several; fundamentally, it is a job, and the worker is worthy of his hire. Moreover, our hospitals should be servants and not masters. Mary Wheeler, that inspiring soul who was at the head of our great Illinois School of Nursing, taught her nurses that the patient came first—first, last and all the time. This thought should be engraved over the entrance of every hospital, together with Laughlin's:

> "Within these gray walls Life begins and ends.
> Here, in this harbor, worn, seaweary ships
> Drop anchor, as the fading sun descends
> And new launched vessels start their outbound trips."

Recently I have had the privilege of lecturing in medicine to the residents at our splendid Veterans Hospital at Hines. Here are alert residents, excellent attending men, unexcelled facilities and a real spirit of learning. The job of diagnosis engages many individuals. The results fully support the feeling of experienced practitioners that physical diagnosis, observation, palpation, and complete examination have lost nothing in the progress of medical science but have been only augmented by the innumerable new tests, techniques and highly specialized methods of the laboratory. There remain a certain number of patients

in whom all of our combined methods seem unable to solve the intricate buried problems of diagnosis.

I see in our audience many wives. There are certain stories about the origin of woman. There is the old Biblical one of the origin of Adam and Eve. There is the Phoenician story of Pygmalion and Galatea—that woman was carved from precious ivory by man and touched with the essence of life by Aphrodite. There is the more intriguing story of the Greeks that Zeus in an off moment gave a directive to Vulcan to model woman out of clay and then in a nasty moment encouraged all the lesser gods and goddesses to hang on every one of their bad qualities as decorations; and so the poor woman became passionate and frigid, dry and wet, hot and cold, vivacious and depressed, by evening beautiful, by morning frayed, capricious and steady, cooperative and stubborn. The Scandinavians dressed the story up. The three sons of Bor were beachcombing, when they came upon two sticks, one of ash and the other of elm. The boys began to whittle on the sticks and from the ash came man and from the elm, woman.

Regardless of the manner in which you lovely ladies came about, or had origin, the world is better for it. The Bible says that the meek shall inherit the earth, but I am sure that this constant has been changed and we must now report, "Blessed are the widows for they already have it." I am sure that these doctors, one and all, acknowledge your loyalty, patience and interest, in spite of the necessity of converting your absorptive brains into a professional ash can containing Smith's hernia, Rebecca's diabetes, Mrs. O'Brien's hemorrhoids and Ole's gall bladder.

In the days to come, the physician of experience will probably be put at the end of the line, as Lipscomb has suggested, there to gather in the many and diverse results of the increasingly diverse examinations; he will have to correlate them, extract the important points, make the diagnosis and then take time to talk with the patient and convey the essence of a program of activity or rehabilitation, fully cognizant of the personality of the patient as a living individual.

And so we revert to our idea—to treat the sick, whether young or in the age group to which you are now giving attention, is a wonderful job——the job of educated professional gentlemen.

Current Geriatric Literature

THE PSYCHIATRIST'S ROLE IN THE CARE OF THE AGING.
E. B. Allen and H. E. Clow.
Geriatrics **7:** 117–122, 1952.

After long experience, psychiatrists may come to appreciate that they play imperative roles in the care and treatment of the aging.

Nonpsychotic cases of senescence, cerebral arteriosclerosis, or simple senile dementia may be treated without psychiatric advice. Toxic deliriums of short duration can be treated in general hospitals—in special sections, where noise or disordered behavior does not disturb nonpsychotic patients. However, under such conditions unforeseen factors may arise, and psychiatric insight can prevent distressing complications. This may be done by a psychiatrist to the advantage of both the patient and his family.

THE HEART AND ITS MANAGEMENT IN THE ELDERLY PATIENT.
L. F. Bishop.
Med. Times **80:** 23–30, 1952.

The management of the heart in the elderly patient is a special problem touching almost every branch of medicine.

Improvement in environment in the older age group might appreciably lower death rates in cardiovascular diseases.

Hypertension associated with arteriosclerosis is frequent in the aged. However, high blood pressure in old people often seems to run a rather benign course. Elevation of systolic pressure alone, with normal diastolic pressure, is observed particularly in atherosclerosis. This is a common accompaniment of advancing age, being due to the loss of elasticity in the large arteries. The chief underlying factor of myocardial insufficiency in advanced age, is sclerosis of the coronary arteries. Myocardial ischemia with myocardial infarction and replacement fibrosis constitutes the actual damage.

Control therapy and retardation of progressive cardiac disease must be the prime objectives in the care of the aged. However, aging persons may react differently to therapy than do younger people. In diagnosis and treatment the entire body and mind must be considered an integrated unit. Drugs, diet, rest, exercise and psychotherapy are prime defenses employed by the doctor.

Eliminations in the aging patient must be watched. Favorite remedies are usually firmly established and should be respected. Exercise such as massage, respiratory exercises or resistive movements leading to graded walks, is recommended. There is no question of the psychologic benefit of such a program.

AGED AND CHRONIC SICK. Editorial.
Med. World, London **76:** 4–5, 1952.

In England the absolute and relative proportion of the aged to the rest of the population is 1:6. It is stated that because of the steady advances in medical research, it is likely to become 1:4 within the next twenty-five years.

Formerly geriatricians were concerned with the rehabilitation of the chronically ill and with studies of the physiologic processes of aging. They were not interested in the period of stay of these patients in the hospital nor in their special needs. Today these physicians realize that many important clinical problems center around the elderly sick.

They, therefore, concentrate not only on the common disorders of old age, but also on the group of iatrogenic maladies resulting from prolonged confinement in bed.

Several years ago it was observed that only 1.16 per cent of the aged population was admitted to hospital institutions. Therefore, the problems pertaining thereto will ultimately have to be solved by studies undertaken at the home of the aged chronic sick.

Professor A. P. Thomsen in his Lumleian lectures deals with certain problems of hospitalization and domiciliary care. A plea is made by him that the aged be no longer kept in so-called chronic beds of long-stay wards.

Prevailing conditions prompted Brooke of St. Helier's Hospital, Carshalton, to treat the majority of aged patients in the out-patient department, with transport facilities provided; and to admit only certain types of cases into hospital wards.

Pemberton and Joan Smith advocated the institution of a home social and medical service. In a future medical service there should not exist a rigid distinction between hospital and home treatment, or medical and social care. This is to be accomplished by a closer co-operation between the general practitioner, specialist and M.O.H. The practitioner should be given adequate facilities and the right to summon the full co-operation of the specialist, M.O.H., social welfare authority and hospital.

CHRONIC PSYCHOGENIC HYPERVENTILATION.

S. B. Guge, J. Gabbard, A. Roos and G. Saslow.
Inst. of Living. **10:** 264, 1952.

The frequency of the acute hyperventilation syndrome in patients of a psychosomatic clinic is reported. It occurs mostly in situations of emotional or physical stress. Usually hyperventilation forms part of generalized personality dysfunction, chiefly anxiety neurosis or hysteria. To hyperventilate continually, the patient must respire in the presence of greatly decreased chemical stimuli.

A case in a male aged 66 is described. The patient suffered from dyspnea, palpitation, faintness and dizziness. The usual treatment with a low-salt diet, digilanid and injection of a mercurial diuretic was not successful. The diagnosis made at the clinic showed that the patient was suffering from severe anxiety neurosis. It also revealed the patient's exaggerated concern about his heart condition. Physiologic study showed lowered plasma carbon-dioxide pressure and plasma bicarbonate. Elevated pH was diagnosed as being due to respiratory alkalosis. Compensatory electrolyte shifts involved the chlorides. The acid-base balance changes were similar to those seen in the usual hyperventilation syndromes. Evidence that the fundamental alteration in hyperventilation is lowered CO_2 pressure, was given by reversion toward normal of all shifts.

During hospitalization attention was drawn to the patient's respiration. He was thoroughly instructed in measures to forestall the hyperventilation, and he recovered completely.

RESUMÉ OF THE RESULTS OF CHANGES IN THE PERIPHERAL NERVOUS SYSTEM OF THE AGED. (ZUSAMMENFASSENDE ERGEBNISSE ÜBER ALTERSVERÄNDERUNGEN AM PERIPHEREN NERVENSYSTEM)

H. Hermann.
Ztschr. Altersforsch. **6:** 197–214, 1952.

During the course of life the peripheral nerve cells of man and animal undergo important structural changes. However, the alteration in their form does not take place in all the ganglion cells at the same time. Neither does it occur in all cells with equal intensity. This is why, in the ganglia of men of different ages, more or less perfectly developed nerve cells may be found. However, the rapidity of the development of the individual ganglion cell diminishes with increasing age.

Through careful examination of specimens of peripheral ganglia, diagnoses of age can

be made. This may be accomplished by means of a number of tests involving different microscopic slides. The degree of degeneration of the nerve cells, as well as the difference in the stage of their development must be considered.

The relation of the myelin (plasmodium) sheath, surrounded by the neurilemma, to the nerve cells is also of importance. Terni has been successful in determining the age of several individuals in this manner. Therefore, the age of man can be determined from the morphologic picture of the nerve cells. However, with certain restrictions, the more advanced a person's age, the more difficult is the determination by this method. Sometimes the ganglia of a man aged 60 have the appearance of those of a person aged 80.

Aging is a process which in every individual advances with different rapidity. This is evidenced also by the fact that greying of the hair occurs in certain people much earlier than in others.

A CASE OF ARTERITIS TEMPORALIS TREATED WITH ACTH.

H. P. Ø. Kristensen.

Acta med. Scandinav. **142:** 391–397, 1952.

A lesion of this type involves universal arteritis. Occurrence in the temporal artery must be looked upon as a mere symptom. The presence of non-characteristic febrilia with vague universal symptoms in elderly persons may be due to "atypical" arteritis temporalis.

The patient under observation was a female, 71 years old, suffering from a typical case. Markedly increased sedimentation rate and moderate anemia were associated with a low value for serum iron.

Antihistamine (amidryl) and aureomycin had no effect on the patient's condition. ACTH produced a prompt and favorable effect. The pain subsided, temperature and sedimentation rate decreased, and the patient's general condition improved. When ACTH was discontinued, the temperature became again subfebrile, and the sedimentation rate rose to the former level. After continuation of the therapy, pronounced improvement was observed. Two months later the patient was discharged, feeling fairly well, but with a slight subfebrile temperature.

The Mayo Clinic has reported 2 cases treated with cortisone, which caused prompt relief from local and universal symptoms.

ACTH intermittent treatment, associated with dicoumarin therapy, may prevent the affection from developing in vital vascular regions.

AGE CHANGES IN THE MAXIMAL RATE OF RENAL TUBULAR REABSORPTION OF GLUCOSE.

J. H. Miller, R. K. McDonald and N. W. Shock.

J. Gerontol. **7:** 196–200, 1952.

The maximum capacity of the renal tubule to reabsorb glucose from the glomerular filtrate diminishes with age, in a linear manner. This was observed in a group of 76 males aged 24 to 86 years, tested by standard clearance methods.

The filtration rate at elevated plasma glucose levels decreased from a mean of 146.0 cc./min./1.73 sq.M. in the third decade, to a mean of 81.0 cc./min./1.73 sq.M. in the ninth decade (r: −0.71).

The over-all values fell from 358.7 mg./min.1.73 sq.M. surface area in the third decade, to 219 mg./min./1.73 sq.M. in the ninth decade (r: −0.61).

The rate of decline in the ability to reabsorb glucose was approximately the same as the rate of decline of other renal functions. It is suggested that the nephron loses its function as a unit.

Thus, decreases in random variability with age paralleled those in mean values for filtration and tubular reabsorption occurring with age.

PRIMARY TUBERCULOUS PLEURAL EFFUSION IN OLDER AGE GROUPS.

R. F. Robertson.
Brit. Med. J. No. 4750; **1:** 133, 1952.

Problems relating to the frequency and prognosis of primary tuberculous pleural effusion in older age groups are elucidated. In a series of adults aged 40 to 80, with serous pleural effusion, one third had serous tuberculous effusion. In the remainder the effusion proved to be secondary to other conditions. Approximately 10 per cent of all primary tuberculous pleural effusions occur in adults between the ages of 40 to 80. The etiology of this disease in the aged is discussed in relation to delayed primary infection, or a "second" primary infection. The latter seems rather unlikely. Difficulties in assessing the prognosis of primary tuberculous effusion in the older age groups are reviewed. The present investigation suggests that subsequent tuberculous morbidity is greater in the aged than in younger adults. The foregoing has been proven through re-examination of the patients in question, after from three to six years. This showed unfavorable development, mostly into intrapulmonary tuberculosis, in about one half of the aged patients. In many cases it led to a fatal issue.

ANTIHEMORRHAGIC EFFECTS AND THEIR INDIVIDUAL FACTORS AT DIFFERENT AGES. (DAS BLUTSTILLUNGSVERMÖGEN UND SEINE EINZELNEN FAKTOREN IN DEN VERSCHIEDENEN ALTERSKLASSEN).

F. H. Schulz.
Ztschr. Altersforsch. **6:** 295, 1952.

A report is submitted with regard to the factors and effects of staunching wounds. Reference is made to antihemorrhagic influence, dependent on increasing age. According to findings, in patients of different ages various factors come into consideration. The time of reaction, the capillary resistance and the amount of albumen diminish with increasing age. The prothrombin potential, the thrombocytes and the duration of the hemorrhage do not change. The amount of fibrinogen and also the globulin quotient show a pronounced increase in patients of advanced age.

Thromboplastin effect depends on the age of the brain. Tests were made with dry thrombokinase, used locally in the treatment of hemorrhage. In this case it was produced from human brain and showed decrease of effect with advancing age.

It has not been ascertained as yet what compensatory processes cause the tendency toward the unchanging antihemorrhagic effects in patients of identical age.

THE 1953 MEETING OF THE AMERICAN GERIATRICS SOCIETY

The 10th Annual Meeting of the American Geriatrics Society will be held at the Hotel Commodore in New York City, May 28–30, 1953.

All members who plan to attend the meeting should reserve accommodations at the Hotel Commodore at an early date. The meeting is being held just before that of the American Medical Association and the hotels expect to be filled to capacity.

The Annual Dinner of the Society will be held on Friday evening, May 29, at 7:30 p.m. preceded by cocktails at 7:00 p.m. Wives and guests of members are welcome.

The Annual Business Meeting will be held Thursday, May 28. The time of this meeting will be announced later.

NATIONAL ADVISORY COMMITTEE ON INDUSTRIAL EMPLOYMENT OF OLDER PEOPLE

The National Advisory Committee on Industrial Employment of Older People, a committee of the American Geriatrics Society, has available literature on work performance of older people, physical capability *vs.* job requirement evaluation techniques, and disability job placement tables. Any physician interested in receiving this information may do so without charge by writing to the chairman of the committee, Dr. George C. Dowd, 216 Main Street, Worcester 8, Massachusetts.